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PATHOLOGY*

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YOU HAVE BEEN TOLD by your previous teachers that their particular subject is the most important in the entire medical course. They are honest men and no doubt they believe what they said. But they were mistaken. The most important subject, of course, is pathology.

Just as anatomy and histology are the study of the normal body, gross and microscopic, and as physiology is the study of the working of the body in health, so pathology is the study of the structure and function of the body in disease. Disturbance in structure we call lesions, which means injuries; disturbance in function may show itself as symptoms of disease, or it may not be recognized for a time, either by patient or doctor because of the remarkable compensating power of the body as a whole and of its individual organs in particular.

You are going to spend the whole of your professional lives looking after diseased bodies. It may, therefore, seem to you not unreasonable and far-fetched when I say that pathology is for you the most important of all the subjects in the curriculum.

You will soon find that pathology is a bridge between the preclinical sciences and clinical practice. It concerns structure, function, causation, which we call etiology, the way in which causes operate, which we call pathogenesis, and finally end results. The most interesting act in a play, the vital chapter in a detective story, is the final one. In pathology, the final act is played, the last chapter is read in the autopsy room. It is at the post-mortem that everything which has been vague and confused often becomes clear for the first time. The greatest masters of clinical medicine, with Osler at their head, were constant attenders at the autopsy which so often laid bare the whole story of their patient's illness.

You must therefore see as many autopsies as possible. And this is of particular importance, not so much when you are students in the pathology course, but when you are in the clinical years, even more when you are interns, and most of all when you have patients of your own.

You think that you can learn pathology by coming to hear lectures on the subject. There could not be a greater mistake. You learn anatomy in the dissecting room, not in the lecture hall. You learn pathology in the pathology museum, in the autopsy room, and in the laboratory looking down the micro-

*Introductory lecture, University of British Columbia, September 7, 1951.

scope at the lesions produced by disease. In my museum at Toronto I put up a large notice which read: "Look! Never mind what's in the book!" Unfortunately we have no pathology museum in Vancouver at the moment, so that you *must* mind what is in the book.

That brings us to the subject of textbooks of pathology. The four best books are by MacCallum of Johns Hopkins, who is now dead, Anderson of Milwaukee, Karsner of Cleveland, and Moore of St. Louis. The fifth best book is by Boyd of Vancouver. As this is the book which I myself use, you may find it advisable to use it also.

There are two parts to a book: one is the letter press and the other is the pictures. I find that the student welcomes pictures with delight, particularly one which fills a whole page. He turns over that page with relief, feeling that there is nothing he needs to learn on it. But he is profoundly mistaken. In the first place, the author has taken great trouble to make that picture, and, in the second place, it is much easier to remember a picture than to remember the words of a paragraph or a page. A zoology student once wrote seven pages of description of an animal in an examination in the morning, but failed to recognize the beast when shown it at a quiz in the afternoon. If he had looked at a picture, he would have been saved.

You may have heard the saying attributed to a medical student: "Mine not to think and look; mine but to know the book." In this class, I want you to learn not only to look, which is not easy, but also to think, which is far harder. But if you can't learn to *think* about pathology, you can't hope to become a good doctor. When a clever doctor examines the patient and makes a correct diagnosis, he is really thinking of the pathological lesion, even though that is hidden deep within the body. The poor doctor only diagnoses fever or pain and ties a label to it. Remember that you do not come to the university to be taught, but to learn, which means that you have got to teach yourself. Canned food is all right in camp, but you want something better at home. So it is with canned food for the mind. You will never make a good doctor if you are content with that sort of nourishment. So you have to think out things for yourselves. The best way to learn to think about a subject is to have to answer questions. I therefore propose to ask you questions throughout the lectures and the lab classes. These will stimulate you to think. It may also stimulate and amuse the rest of the class who are listening to you. Education has been defined by a cynic as that process by which the contents of the professor's notebook reaches the notebook of the student without disturbance of the mind of either. Questions and answers are calculated to produce disturbance in the minds of both. These questions will be on the pages of the book to be covered for that day. You will therefore have to read the subject before, rather than after, the lecture. I tried this method with much enjoyment during my last year or two in Winnipeg, but had to give it up in Toronto because of the huge size of the classes. Perhaps the superior quality of the U.B.C. students may also help to make the Socratic method more successful! You will see, therefore, that I am not going to try to teach you pathology; I am going to try to teach you how to learn pathology. We must recognize the difference between training and education. You can be *trained* to do an operation

perfectly, but you must be *educated* so as to know when an operation should be done.

Our subject is divided into General Pathology and Special Pathology, and you will find this division in your textbook. Of these two, by far the more important is general pathology. This branch of the subject is the study of the general processes of disease, such as inflammation, interference with the blood flow, and tumour formation. Special pathology is the application of this knowledge to the individual organs and tissues. If you already know the fundamentals of inflammation, which you learn in general pathology, you need spend little time when you come to special pathology in the study of pleurisy, which is inflammation of the pleura, pneumonia, which is inflammation of the lung, appendicitis, which is inflammation of the vermiform appendix, or abscess of the brain, which is the result of localized inflammation of that organ. All you have to do is to apply the general principles to the individual instance. But you must do that by thinking, not by memorizing.

In general pathology you will learn that thrombosis is a special form of clotting which takes place in the flowing blood. You will learn that ischaemia or the complete cutting off of the blood supply to a part results in necrosis or death of that part. So if I suddenly ask you what is the effect of thrombosis of the coronary artery, the superior mesenteric artery, or one of the cerebral arteries, you will be able to give me the correct answer in general terms. A portion of the myocardium, the bowel, or the brain will die. Unfortunately, the actual changes in the necrosed tissue in these three sites is entirely different, and you will have to learn these differences. So you see that in special pathology you cannot merely sit in your armchair and apply the principles of general pathology. You must see for yourselves the lesions, both gross and microscopic, in the different organs.

So it is with cancer. In general pathology you will study the general laws governing the spread of tumours, and you will learn that cancer may spread far and wide through the tissue spaces, by the lymphatics and by the blood stream. That is well and good as far as it goes, yet in special pathology you will find that cancer of the lung and prostate obey the rules, but that cancer of the skin does not spread to a distance for a long time, that cancer of the tongue spreads with great rapidity, and that cancer of the brain never spreads outside the skull. You can see how important it is for you to know these facts when a patient with cancer trusts himself to your care. A moment ago I used the word never. You should never say never in pathological matters, because the possibilities of disease are so endless that anything may happen. But if you want to be a successful doctor, you should make a practice of diagnosing sparrows rather than canaries, for then you will usually be right.

General pathology may be compared with grammar in the study of language and the practice of scales in the study of music. The only difference is that grammar and scales are dull and wearisome, whereas general pathology is delightful and fascinating.

It has been said that "histology is an odd-tasting dish, repulsive as a medicament to students who must be examined in it. Taken in large quantities under compulsion it is not absorbed, but if

tasted repeatedly in little sips it finally becomes a delight to the palate and even a cause of addiction". That is not true of pathology, where even large draughts are refreshing and stimulating. But it is the case that you will now find a new interest and use for histology. In pernicious anaemia the gastric mucosa becomes thin, but how can you tell if it is thin unless you know the normal thickness. In chronic Bright's disease great numbers of glomeruli disappear, but to appreciate that you must have some idea of how many glomeruli there should be in a low-power field. In poliomyelitis there is a wiping out of the motor nerve cells in the anterior horn, but again you must know the normal appearance of that horn. If a man has a supp. in pathology, I always think that it would do him good to have a supp. in histology also.

In our studies together I would like you to acquire a respect for and an appreciation of the words that you use. Do not say "the spleen appears to be enlarged" when it is ten times the normal size. The words "appears" and "seems" indicate doubt; they are therefore favourites with students who do not wish to commit themselves and go too far out on a limb. After all, you would not say: "The patient appears or seems to have lost his right hand". And please shun the word "shows" in your written descriptions of microscopic appearances. You have no idea how irritated I become when I read that in a section of the kidney the glomeruli show swelling, the tubules show atrophy, and the arteries show thickening. Use simple words. The glomeruli are enlarged, the tubules atrophic, and the arteries thickened. Avoid high-flown phrases to describe simple conditions. To write: "He was conveyed to his place of residence in an intoxicated condition", is to use jargon, when all you need to say is: "He was taken home drunk".

I hope that you will enjoy yourselves during the time you spend with us. But do not think for a moment that you are finished with pathology on the day you pass the final examination of this department. You won't be a pathologist when you finish this course any more than you will be a par golfer when you have finished a course of lessons with a pro, no matter how good that pro may be.

Whenever you start to study medicine, surgery and gynaecology you will have to turn to pathology and you will begin to realize the gaps in your knowledge. You will be horrified to encounter questions on pathology in the examination papers of the three clinical subjects which I have just mentioned. If you do not have the ability necessary to become a good family doctor, you may have to become a specialist. Now you cannot become a qualified specialist unless you pass an examination for certification in that specialty some five or more years after graduation, or the examination for the Fellowship of the Royal College of Physicians and Surgeons. I hate to tell you this, but in both these examinations there is a paper and an oral in pathology! You will understand that you cannot shut the door on pathology at the end of this course. Indeed, if you decide to take the post-graduate training to enable you to become a surgeon, an internist, or a gynaecologist, you will find that a year's internship in a department of pathology is the most valuable way you can spend your time. If you do not

believe me, then ask the professor of medicine, or surgery, or of obstetrics and gynaecology.

I have said that I think and hope that you will find pathology interesting as well as useful. Perhaps it may prove so interesting that one of you may decide to take it up as your life's work. If you do, you will never regret it. And if you do regret it, you will find that the training has fitted you for any other branch of medical practice.

WHAT IS YOUR DIAGNOSIS, DOCTOR?

A number of pathological conditions have certain feature about them that are almost pathognomonic. Here are twenty descriptive terms that should suggest, to the well-versed student, specific lesions or diseases.

1. Sulfur granules
2. Dinner-fork deformity
3. Currant-jelly stool
4. Nutmeg liver
5. Melon seed bodies
6. Black vomit
7. Scissor gait
8. Leather bottle stomach
9. Donovan bodies
10. Sabre shin
11. Hobnailed liver
12. Rice-water stools
13. Flea-bitten kidney
14. Onion skin (X-ray of bone)
15. Policeman's tip
16. Risus sardonicus
17. Poker back
18. Sago spleen
19. Saddle nose
20. Butterfly rash

Answers on page 119.

AN INTRODUCTION TO THE COLLAGEN DISEASES

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"Collagen disease" is a term which has been introduced into the medical literature of the last decade, designed to bring together a group of illnesses which appear to have certain features in common with one another It has been done primarily in an attempt to elucidate and promote a better understanding of the pathological processes involved and the etiological factors concerned in the production of these changes, many of which show a striking similarity, involving as they do chiefly the collagenous or supporting tissues of the body. The present article is an attempt to evaluate the meaning and status of the term collagen disease based on a review of the literature.

The following case history is reproduced from the report by Kampmeier (13) as indicative of the complexity of the problem, illustrating as it does the overlapping of features common to all of the diseases in this group, both clinically and pathologically.

CASE HISTORY

In May 1946, a 33 year old white woman was admitted to Vanderbilt University Hospital in Nashville, Tennessee and died within two hours. She had been in the University hospital on two previous occasions and gave the following history.

In 1939, one day following a normal delivery, she noted the onset of malaise, anorexia, fever and aching which soon localized in the joints. After two weeks, the knees, ankles, elbows, wrists and finger joints became painful, swollen and red. She suffered from recurrent attacks of a similar nature every three to six months, each lasting two to three weeks. Painful subcutaneous nodules appeared near the affected joints. During 1942 she had a brief illness labelled as "pleurisy" and the following year noted the onset of ankle edema when up and about on her feet. She was first admitted to hospital for these complaints on May 5, 1944.

Examination showed pigmentation of the skin. There was scarring on the forehead and temporal areas. The skin of the hands was atrophic. Nodules two to three mms. in diameter were noted at several sites along the tendons. Most of these were at the wrists and on the hands. The only cardiac abnormality was an accentuated pulmonic second sound. The Electrocardiogram showed slurring of the QRS complex with right axis deviation. X-ray examination demonstrated atrophy of bone in the neighbourhood of the joints.—Hb.—12 gms.; W.B.C's—3500/cu. mm.; E.S.R — 34 mms.; eosinophiles — 2%; Lymphocytes—35%.

Biopsy showed chronic (rheumatoid) tenosynovitis and chronic inflammation of the skin. During the hospital course the daily temperature ranged from 98.6 to 100 F.

Her second admission was in Nov., 1945. Attacks of arthritis had occurred as before associated with fever as high as 103 F. She stated that for more than a year previously she had noticed a red roughened patch of skin especially over the elbows, which healed with scarring. The rash extended to the wrists, hands, neck and face. Physical examination revealed a blotchy, purplish, erythematous eruption with scarring over the extensor surfaces of the arms, and a "butter-fly" pattern over the nose and cheeks. By this time there was cardiac enlargement, an accentuated pulmonic second sound and a diastolic murmur at the third, left interspace. X-ray study showed an enlarged heart and pulmonary conus. A biopsy

again demonstrated inflammation and scarring of the skin. There was no change in the laboratory findings.—Serum protein —7.48 gms.%, serum albumin—3.76 gms.% — serum globulin—3.72 gms.%. During her stay in hospital her temperature ranged between 98.6 and 99.4 daily.

The following information was obtained during her third (and last) admission. She had been bedfast for 1 month with anorexia and generalized pain, having gained twenty lbs. in weight due to edema and ascites. The clinical diagnosis at this time was disseminated lupus erythematosus; pulmonary hypertension and right heart failure.

At autopsy the significant findings could be classified as characteristic of various clinical disease states as indicated:

Endocarditis (nodules on tricuspid and mitral valves)—
Libman-Sachs disease
Pericarditis (adhesive)—
Rheumatic infection
Pulmonary arteriolitis—
Periarteritis nodosa
Chronic inflammation of skin—
Scleroderma
Skin and muscle lesions—
Dermatomyositis
Arthritis and tenosynovities—
Rheumatoid arthritis
Facial skin lesions—
Disseminated lupus erythematosus

As indicated in table 1, it would appear that many clinical manifestations are common to the diseases listed above. The introductory case report has shown that an illness may at first seem to represent one of these diseases and later in its course, assume the characteristics of another. This confusion is illustrated throughout the literature and also in the minds of clinicians and pathologists who insist that they are unrelated entities, yet talk about "transitional" cases.

TABLE I

Clinical Characteristics*	Disseminated Lupus	Periarteritis Nodosa	Dermato-myositis	Sclero-derma	Rheumatoid Arthritis
1—abrupt onset commonly	+	+	?		
2—age	sex phase	any	any	any	any
3—sex	F > M	M > F	M > F	F > M	F > M
4—course (wks-mos)	+	+	( )	( )	( )
5—course (years)	+	( )	+	+	+
6—recovery	rare	rare	occ.	rare	some
7—fever (chills)	+	+	+	+	+
8—malaise, asthenia	+	+	+	+	+
9—wt. loss	+	+	+	+	+
10—arthralgia. myalgia	+	+	+	+	+
11—tachycardia	+	+	+	+	+
12—abdominal discomfort	+	+	+	( )	( )
13—anemia	+	+	+	+	+
14—increased sed. rate	+	+	+	+	+
15—leucocytosis	0-+	0-4+	0-4+	0-+	0-+
16—eosinophilia	( )	+	+	( )	( )
17—associated skin lesions	+	+	+	+	+
18—photosensitivity	+	( )	+	( )	( )
19—lymphadenopathy	+	+	+	+	+
20—subcutaneous nodules	+	+	+	+	+
21—arthritis	+	+	+	+	+
22—oral lesions	+	( )	+	( )	( )
23—pleuro-pulmonary	+	+	( )	( )	( )
24—pericardial	+	+	+	+	+
25—myocardial	+	+	+	+	+
26—valvular	+	+	+	+	+
27—coronary	+	+	+	( )	( )
28—renal	+	+	+	+	( )
29—hepatic	+	+	( )	( )	( )
30—splenic	+	+	+	( )	+
31—muscle	+	+	+	+	+
32—nervous system	+	+	+	+	+

*all are not present in every case.

THE CONCEPT OF COLLAGEN DISEASE

The Thesis of Morgagni (1) that diseases reside in certain organs of the body has dominated pathologic anatomy and clinical investigation for centuries. The great advance of medicine throughout the 19th century was the development of the method of correlation of post-mortem observations with those made on the hospital wards. This clinicopathologic concept was further advanced by the recognition of an interdependence and unity of certain organs to form organ or tissue systems. But one cannot justly maintain that an essential site can be demonstrated in every disease; for example, certain acute infections and intoxications do not produce characteristic or significant lesions in any organ. Another difficulty with this theory is that in certain diseases, rheumatic fever, for instance, apparently unrelated organs are the sites of the morbid processes.

Klinge and his school in 1933 were the first to propose that rheumatic fever and rheumatoid arthritis reflected a systemic involvement of the entire connective tissue of the body. The occurrence of similar connective tissue changes in rabbits made hypersensitive to foreign proteins (Gerlach and Klinge) led him to believe that the tissue damage in human rheumatic disease was due to hypersensitivity. Consequently he maintained that the same pathogenetic mechanism applied in other disease entities characterized anatomically by fibrinoid change, so he included in the group the following: periarteritis nodosa, malignant nephrosclerosis, thromboangiitis obliterans, dermatomyositis, certain nephritides and sub-acute bacterial endocarditis.

The apparently heterogeneous organ lesions in disseminated lupus erythematosus have similarly been shown to be the result of a fundamental alteration of the collagenous tissues. These collagen alterations are in most individual observations more widespread and conspicuous than those in rheumatic fever, affecting with particular frequency the collagen framework of the heart and of small blood vessels and capillaries, especially those of the kidneys. The connective tissue of the mediastinum and retroperitoneal space may also be affected. It is reasonable therefore to consider these maladies as "systemic diseases of the connective tissues".

The justification for the concept of a systemic disease of connective tissue depends on the actual existence of a connective tissue system. A system is, in the biologic sense, an assemblage of organic structures composed of similar elements and combined for the same general functions. The connective tissue proper can then justly be regarded as a system because it consists, throughout the body, of an association of similar cellular and fibrillar elements held together by a third component, an amorphous ground or cement substance. The colloidal nature of this ground substance has been stressed by Schade (1) and later by Klemperer. Obviously these elements are combined not only for the general function of support but also for the regulation of salt and water balance and as the site of transfer of metabolites, due to their being situated between the parenchymal cells and the canalicular blood and lymph spaces of the body.

Klemperer et al (1), first became aware of the disorder of the connective tissue as a system in their studies of disseminated lupus erythematosus. The ap-

parent heterogeneous involvement of various organs in this disease had no logic until it became apparent that the widespread lesions were identical in that they were mere local expressions of a morbid process affecting the entire collagenous tissue system. The most prominent of these alterations is fibrinoid degeneration—a descriptive, morphologic term indicating certain well defined optic and tinctorial changes in the collagenous fibres and ground substance. The straightening and thickening of the collagen fibres, their apparent friability, their intense eosinophilia and refractibility, together with visible increase in the ground substance can be due only to a profound physico-chemical aberration of the colloid state of the connective tissues.

In diffuse scleroderma, the collagen disturbance is manifest not only as fibrinoid degeneration, but also as an increase of bulk and density of the connective tissue. It is evident, then, that fibrinoid degeneration and collagen sclerosis are the morphologic expression of different phases of a disturbed colloidal collagen system.

In these two diseases, morphologic alterations may in the individual case be indeed striking, but even here the changes are hardly crucial enough to account for the profound clinical debasement and death of the patient. This is even more impressive in some cases in which the characteristic morphological indices of a systematic collagen disturbance are discoverable only after the most minute search. How can one account for such a discrepancy? It is unlikely that other tissue changes have been overlooked or not comprehended. In the fully developed case the morphologic signs of implication of the collagenous tissues are quite clear. The fact of total involvement of the collagen tissue system is also quite clear. Can we assume therefore that a derangement of the colloidal state of the system exists even though it cannot be consistently revealed by our histologic methods? MacCallum has already made this assumption (1) in analysing a case of acute scleroderma in an eighteen year old boy. We must also assume this in scleroderma adultorum where the hardening of the skin is far out of proportion to the demonstrable histological alteration. Moreover, the clinical reversibility of the condition lends credence to the view that the alteration is due to a transient colloidal imbalance within the collagenous tissues.

One may therefore apply the term "diffuse collagen disease" to acute and chronic maladies which are characterized anatomically by generalized alterations of the connective tissue, particularly by abnormalities of its extracellular components (Klemperer, 1942). In this sense the term can include rheumatic fever, rheumatoid arthritis, periarteritis nodosa, disseminated lupus erythematosus, scleroderma and dermatomyositis.

PATHOLOGY

Fundamentally the pathology in all the diseases mentioned is one of tissue derived from mesoderm. Normally the ground substance or collagenous intercellular material is invisible. In these diseases there is swelling, increased density and fibrinoid change,* in terms of the staining quality of the collagen.

*The term "fibrinoid collagen change" or "fibrinoid degeneration" as originally applied by Newmann (1) referred to collagen fibres which assume the structural and tinctorial qualities of fibrin.

Furthermore these areas are infiltrated with polymorphonuclear leucocytes and round cells (lymphocytes and plasma cells). Eosinophiles may be present. Fibroblasts and histiocytes show variable activity.

The vascular lesions result from these connective tissue changes which occur in the media, adventitia and perivascular tissues. These changes may be degenerative on the one hand, or may show great inflammatory activity with necrosis. Thus, fibrinoid necrosis in the media of an arteriole, proliferation of the intima, and perivascular infiltration, may be so destructive as to lead to aneurysmal formation as in periarteritis nodosa. This is often named a necrotizing arteritis and characteristically affects the larger arterioles. In disseminated lupus erythematosus, fibrinoid material appears in the several layers of the vessel wall, of such extent that destruction of all portions occurs even to occlusion of the lumen. Focal capillary changes appear especially in the kidneys.

In both dermatomyositis and rheumatoid arthritis, the skeletal muscles will be found to be pale, with edema and loss of striation of the muscle fibres. There is accompanying round cell infiltration which is focal, and in dermatomyositis likely to be perivascular.

Both scleroderma and dermatomyositis show perivascular infiltration with round cells in the subcutaneous tissues as well as proliferation of connective tissue bundles. In rheumatoid arthritis there is lymphocytic infiltration, which may be perivascular as well as non perivascular distributed in the subsynovial tissues. The muscles show a nodular myositis (round cell infiltration) edema and loss of striation of the muscle cells. Rheumatoid nodules demonstrate focal fibrinoid degeneration and necrosis. The clinical characteristics are dependent upon the site of the vascular change, whether renal, pulmonary, pericardial, pleural, endocardial, brain, muscle, skin or joints.

PATHOGENESIS

There are two main schools of thought regarding the pathogenesis of the collagen diseases.

Klemperer (1, 14) states that although fibrinoid degeneration is a common finding in these diseases, he is not prepared at present to accept an allergic basis for these diseases, pointing out that "hypergic inflammation is characterized by fibrinoid degeneration but not always vice versa". Fibrinoid degeneration has been seen under conditions where allergy can be ruled out such as; in the walls of arteries in malignant hypertension; in experimental hypertension where it is sometimes associated with vascular lesions simulating periarteritis nodosa; in the ischemic kidney, during the Goldblatt experiment (blood supply to kidney decreased); following the injection of bacteria of low virulence and chemical agents into connective tissue; in reacting connective tissue adjacent to a foreign body; in the base of a peptic ulcer; in the vicinity of pancreatic necrosis; in the skin of the rat following trivial mechanical injury; and identical vascular lesions have been produced by Winternitz et al., Holman, Duff and Koletsky under experimental conditions which ruled out hypersensitivity as a factor affecting their pathogenesis.

We are concerned here only with diseases which affect the connective tissue system in its entirety. Among these are disseminated lupus erythematosus and certain cases of diffuse scleroderma.

There are, indeed, other diseases which when analysed are also found to affect the connective tissue system; however, to identify this system as the seat of certain diseases is by no means to identify these diseases with each other or even to relate them. This would be an unjustifiable simplification.

Klinge has shown, for example, that rheumatic fever affects the connective tissue in a widespread manner as does disseminated lupus and scleroderma. All three show fibrinoid degeneration as well, but the glomerular lesions of the latter two diseases are never seen in rheumatic fever and the Aschoff nodule does not occur in lupus or scleroderma. The previous cited experiences lead Klemperer and his school to believe that the connective tissue changes demand further analysis before the question of pathogenesis can be settled.

Rich (3, 4, 5, 7, 11, 12) on the other hand feels strongly that the pathologic changes can be explained on the basis of hypersensitivity of connective tissues. In 1903, it was shown that in the Arthus phenomenon (an unquestioned sensitivity reaction) vascular necrosis and adventitial inflammation are prominent. It has been accepted almost universally since Swift's work in 1929 that rheumatic fever represents both clinically and pathologically an anaphylactic type of response. If one compares the clinical and pathologic findings as appear in table 2, the similarity of rheumatic fever and serum sickness is most striking. In this table from Rich (3) are also listed the findings in experimental serum sickness induced in rabbits sensitized to horse serum.

Thus in rheumatic fever, human and experimental serum sickness, Rich found focal alterations in the collagen of the heart valves, endocardium and pericardium; round cell infiltration in focal areas of damaged collagen and verrucose valvular vegetations. In another paper Rich related the lesions of rheumatic fever and serum sickness (both human and experimental), to similar lesions encountered in disseminated lupus erythematosus.

In 1942 Rich (4) found the lesions of periarteritis nodosa in a number of patients who had died following the combined use of anti-pneumococcic

TABLE II

COMPARISON OF FINDINGS IN RHEUMATIC FEVER, HUMAN AND EXPERIMENTAL SERUM SICKNESS (RICH)

Finding	Rheumatic Fever	Serum Sickness	
		Human	Experimental
Fever	+	+	+
Arthritis	+	+	?
Urticaria	+	+	+
Erythemas	+	+	+
Purpura	+	+	+
Transient paresis	+	+	?
Myocarditis	+	+	+
Valvulitis	+	+	+
Pericarditis	+	?	+
Focal swelling, degeneration of collagen	+	+	+
Lesions of Aschoff body type	+	?	+
Tissue eosinophilia	+	+	+
Necrosis, inflammation of arteries	+	+	+

serum and a sulfonamide. He (5) also described a patient with periarteritis nodosa occurring after transfusions and the administration of sulfonamides post-operatively (the surgical specimen at the time of operation did not show the vascular lesions but the autopsy specimens from the same site did show it). In 1943 French and Weller (6) independently reported their observations on interstitial myocarditis with infiltration by round cells, polymorpho-nuclear leucocytes and eosinophiles in patients who received sulfonamide therapy and subsequently died. The same year Rich (11) stated that rabbits subjected to experimental serum sickness develop, in some cases, cardiac lesions that in their basic characteristics resemble closely those of rheumatic carditis. He and Gregory (12) then reported that typical diffuse periarteritis had been produced experimentally by establishing in rabbits a condition analogous to serum sickness in man. They believe that periarteritis nodosa is one manifestation of the anaphylactic type of hypersensitivity, and they further believe that widely different types of sensitizing antigens are capable of causing this disease in man and they suggest the advisability of attempting to discover and eliminate the responsible antigen in each case diagnosed clinically. The same group (7) also reported an instance of what they termed sensitivity to iodine, in which the patient after several days administration of Lugol's solution developed a fever of 104 F and a blood eosinophilia of 22% and died. At autopsy, periarteritis was found in the internal organs.

Holman (8) demonstrated that a specific (lipid containing) diet fed to dogs, in which renal damage had been produced (by mercury or other chemicals), caused death from uremia. Neither the diet nor renal damage alone caused death. At autopsy he found necrotizing vascular lesions characteristic of periarteritis and rheumatic fever. He related these lesions to sensitization of the tissue to a lipid, and also showed that the lesions were prevented by the use of vitamin E when this was given immediately before or after the institution of renal damage.

RELATIONSHIP OF HYALURONIDASE TO THE COLLAGEN DISEASES

This enzyme attacks hyaluronic acid, a component of the collagen material. If a subcutaneous injection of the enzyme is followed by an injection of India ink, the ink particles extend over a much greater area, than in one not prepared by an injection of the enzyme. This is the "spreading factor" of the experimental literature. It has been shown that certain strains of streptococci and other organisms liberate quantities of this enzyme, so attacking the hyaluronic acid of the collagen, and permitting the spread of foreign material. It is also known that the normal body provides an anti-hyaluronidase (counter-enzyme).

One might speculate about the possibility of the liberation of such an enzyme from infectious agents in the body making the collagen vulnerable to reaction from a foreign substance; or a deficiency in the anti-enzyme permitting the spread of foreign material into the mesodermal tissue structure. Variability in such factors may account for the degree of reaction as well as the site of major change. Just what part hyaluronidase may play in the production of the pathological changes seen in these diseases, if any, is still not clear.

CONCLUSION

Today, knowledge is fragmentary, and the tempo of discovery, rapid. The fundamental problem of fibre formation will be brought to a solution by tissue culture and electron microscopy. The chemical nature of the ground substance, its origin and the influence of enzymes and hormones upon its constitution are under vigorous scientific attack.

The majority of workers in this field are convinced that the concept of collagen disease is not an idle speculation. The increasing interest of the medical profession is evidence of this; but the impatience of clinical investigators and a peculiar worship of diagnostic terms have led to an exaggerated popularity of the diagnosis "Collagen Disease". Klemperer et al. suggested the term in 1942, because of the conspicuous morbid manifestations of the extra-cellular components, in a "pars pro toto" sense. They believe today that even this cautious synthesis was premature because it resulted in an indiscriminate acceptance of a term with a diagnostic and pathogenetic import which was not intended when it was conceived.

There is danger that it may become a catch-all term for maladies with puzzling clinical and anatomic features. It is not a term applicable to diagnosis, and certainly does not define the morbid process of the diseases grouped together. All that Klemperer wanted to express originally was that in certain diseases, anatomical investigations revealed conspicuous alterations of the intermediary substances of the connective tissues in a systemic manner. It seems obvious that alterations of this material cannot be regarded as maladies of these substances, or of the connective tissue as a whole. These morphologic disorders are only outward manifestations of morbid processes, the site and nature of which are still obscure. When further basic research has clarified the factors which control the plasticity of the connective tissues, under normal and abnormal conditions, the concept of collagen diseases will have served its purpose.

In any event this group of diseases is very intriguing. Many readers will wonder why such a fuss is made over "rare" diseases like disseminated lupus, scleroderma, periarteritis and dermatomyositis. However the fact remains that they have been found at autopsy in many patients dying from common cardiac, renal and pulmonary conditions in ever increasing numbers possibly because of the increasing awareness of their existence on the part of the pathologist. Aside from this fact however, does not speculation about these diseases open interesting viewpoints to more common diseases? It is unnecessary to point out what it would mean to the clinician to have knowledge of the pathogenesis of rheumatic fever, and an avenue of attack in the prevention of rheumatic heart disease. How valuable it would be to have definitive information concerning that most disabling of chronic diseases, rheumatoid arthritis.

What bearing may allergic reactions have in glomerulo-nephritis? Klemperer reports an incidence of necrotizing arteritis in the kidney in 10 to 20% of autopsies in sub-acute and chronic nephritis (there is much clinical and experimental evidence for an anaphylactic factor in this disease).

Hypertension is common in periarteritis nodosa. In considering the clinical picture of malignant hypertension, one must realize that necrosis is a common

pathological finding especially of the afferent arterioles of the kidney, less often elsewhere. Surely the similarity of the vascular changes in this disease and periarteritis is more than coincidence.

Finally then, it seems possible that these uncommon diseases spoken of as collagen diseases, actually represent dramatic expressions of a fundamental tissue process responsible for a number of diseases dealt with in everyday practise.

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The training of the medical school gives a man his direction, points him the way, and furnishes him with a chart, fairly incomplete, for the voyage, but nothing more.

WILLIAM OSLER

CLINICAL ASPECTS OF SARCOIDOSIS

A SURVEY OF SEVENTY-FIVE CASES*

ROSAIRE ST. PIERRE, M.D.** AND ARTHUR J. S. BRYANT, M.D.***

Since Besnier[1] described lupus pernio in 1889 and Boeck,[2] in 1899, indicated the characteristic epithelioid structure of the sarcoid skin lesions, many papers have been published on sarcoidosis, particularly in the last ten years. In 1948, an outstanding review of the disease and the literature was reported by Freiman.[3] From this review, and other papers, it is obvious that the solution of most of the problems concerning aetiology, pathogenesis and clinical significance of Boeck's sarcoid still escape complete detection. However, much data have been accumulated from the increasing professional interest and awareness of this condition, and new concepts and better understanding of the tissue reactivity diseases may elucidate the mystery in time.

This paper is a survey of the clinical aspects of the cases diagnosed as Boeck's sarcoid in the records of the Toronto General Hospital, both clinical and pathological. Naturally the details of clinical and laboratory investigations are scanty in those cases which were localized or discovered incidentally at autopsy or on examination of tissue sent from elsewhere to the Department of Pathology. On the whole, however, there is sufficient information to warrant analysis.

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DISTRIBUTION OF CASES BY YEAR, AGE AND SEX

We have collected the records of seventy-five cases in the years 1938 to 1950, inclusive. (See Table I.) During the same period there were some 312,000 hospital admissions. An increasing annual incidence was noted, particularly during the last three years. The cases were spread over all ages from fourteen to seventy-six years, but two-thirds occurred after the age of forty years. The sex ratio was thirty-six males to thirty-nine females. All cases were of Anglo-Saxon origin, except one each of the following races: French-Canadian, Italian, Greek, Polish, Chinese, Japanese and Negro.

Table I

DISTRIBUTION OF 75 CASES (36, MALE AND 39, FEMALE) OF SARCOIDOSIS BY YEAR AND AGE

Year	No. of Cases	Age Decade	No. of Cases
1938	1	10-19	3
1939	0	20-29	8
1940	1	30-39	9
1941	3	40-49	14
1942	4	50-59	14
1943	4	60-69	17
1944	4	70-79	5
1945	6	Not	
1946	6	Recorded*	5
1947	4		
1948	11		
1949	15		
1950	16		
Total	75		75

*In five cases the diagnosis was made on tissue sent to the Department of Pathology; the patients were not admitted to hospital and the ages were not recorded.

GROUPING OF CASES OF SARCOIDOSIS

The cases fell into two main groups: proven (sixty-eight cases) and unproven (seven cases). (See Table II.) The diagnosis was considered to be proven when the characteristic lesion was demonstrated by biopsy in forty-seven cases, and at autopsy in twenty-one cases. The lesion was considered to be characteristic when tissue examination revealed granulomata composed of large, pale epithelioid cells in which were giant cells in varying numbers. There was a minimal peripheral inflammatory reaction. Inclusion bodies were occasionally seen within or associated with the giant cells.

In fourteen cases, the disease was diagnosed clinically on the basis of criteria which are listed below. Pathological confirmation of the diagnosis was obtained in seven of these.

There were twenty-one cases in which the clinical diagnosis was not stated before surgical biopsy revealed sarcoid lesions. (See Table III.) However, seventeen of these were out-patients and all presented non-specific, localized lesions, fifteen being in skin.

In eighteen cases, the disease produced clinical manifestations but the sarcoid nature of the underlying lesion was unsuspected until the pathological examination revealed it. These cases are analysed in Table III. It will be observed that seven of these had localized sarcoidosis; in other patients, specific clinical syndromes like cor pulmonale, portal hypertension, obstructive jaundice, etc. were produced and recognized. In four instances, routine chest roentgenograms revealed the presence of an unsuspected disease process. In three of these, bilateral pulmonary lesions had been diagnosed elsewhere as tuberculosis; this resulted in sanatorium care of these patients for periods varying from eight months to three years. Because the provisional diagnosis was not supported by the clinical course or by laboratory investigation, further studies were conducted and the presence of sarcoidosis demonstrated. The fourth case presented with signs of bronchial adenoma; at operation, gross sarcoid involvement of hilar glands was found.

Apparently asymptomatic sarcoidosis was present in twenty-two cases in which clinical manifestations were related to

TABLE II

GROUPING OF CASES OF SARCOIDOSIS

GROUPS	No. of Cases	Proven Cases*		Unproven Cases**
		Biopsy	Autopsy	
Clinically diagnosed	14	4	3	7
Clinical diagnosis not stated	21	21	0	0
Clinically unsuspected	18	16	2	0
Incidental in other disease	22	6	16	0
Total	75	47	21	7

*Diagnosis demonstrated by pathological examination.
**Clinical diagnosis only.

TABLE III

ANALYSIS OF 18 CASES IN WHICH SARCOIDOSIS WAS UNSUSPECTED CLINICALLY

PROVISIONAL DIAGNOSIS	COMPLAINTS	SITES OF SARCOIDOSIS (*Biopsy or Autopsy*)
1. Rodent ulcer.	Painless lump, lower lip.	Skin.
2. Adenoma of left breast.	Painless lump, left breast.	Breast.
3. Rodent ulcer.	Small nodular mass, forehead.	Skin.
4. Rodent ulcer.	Small lesion, right temple.	Skin.
5. Tumour of left parotid.	Painless lump, parotid area.	Subcutaneous tissue
6. Portal cirrhosis.	Headache, tiredness, nausea, vomiting, haematemesis, enlarged liver and spleen.	Liver and spleen.
7. Hypochromic anaemia.	Menorrhagia, breathlessness, and fatigue.	Heart, lungs, liver, kidneys, pancreas and lymph nodes.
8. Ayerza's disease.	Cough, sputum, wheezing, dyspnoea, constitutional reactions, cyanosis, clubbing of fingers, hydrothorax, peripheral oedema.	Myocardium, lungs, liver, spleen and lymph nodes.
9. Bronchiectasis.	Fatigue, weight loss, cough and sputum, bouts of haemoptysis.	Lungs, spleen and lymph nodes.
10. Cavernous aneurysm.	Tumor, pain Vth nerve. exophthalmos, ptosis.	Orbit.
11. Acne rosacea.	Erythematous diffuse lesions butterfly area, and wart-like lesions; enlargement of lymph nodes.	Skin and lymph nodes.
12. Nasal polyp.	Nasal obstruction and discharge.	Nasal bones—accessory nasal sinuses.
13. Left bronchial adenoma.	Cough and sputum. (Hilar mass picked up on routine X-ray).	Hilar lymph nodes.
14. Advanced quiescent pulmonary tuberculosis.	Constitutional reactions, cough and sputum. (In Sanatorium for three years—abacillary.)	Lungs, lymph nodes and uveal tract.
15. Bilateral pulmonary tuberculosis. (Picked up in routine X-ray)	Cough and sputum. (In Sanatorium for one year—abacillary.) Generalized lymphadenopathy.	Lymph nodes, lungs and cauda equina.
16. Obstructive jaundice.	Painless jaundice, pruritus, pale stools and dark urine, vomiting.	Head of pancreas and regional lymph nodes.
17. Chronic lymphadenitis.	Chronic painless submaxillary lymphadenopathy.	Submaxillary nodes.
18. Bilateral pulmonary tuberculosis. (Picked up in routine X-ray)	Minimal cough and sputum; constitutional reactions. (In Sanatorium for eight months—abacillary.)	Lungs, liver and lymph nodes.

other diseases. In this group, sarcoid involvement of lymph nodes regional to primary carcinoma occurred in five cases. In Table IV are listed the fatal diseases with which sarcoidosis was found incidentally at autopsy; it will be observed that, in seventeen cases, sarcoid lesions were found in a heterogenous group of diseases. The question of the possible association of pulmonary tuberculosis was studied in these cases. In seven, pulmonary tuberculosis was searched for and not found. It was also presumed to be absent in nine others in which the usual autopsy protocol was followed and tuberculosis lesions of the lungs were not mentioned. In one instance only was obsolete pulmonary tuberculosis present and, in this case, sarcoidosis was found only in the liver and spleen.

The diagnosis of the unproven group (seven cases) was clinical only and based on the following criteria:

(a) Evidence of chronic, insidious, extensive disease involving certain groups of organs, such as: lymph nodes, lungs, skin, liver and spleen, together with the frequent absence of significant symptoms.

(b) Presence of the uveoparotid syndrome, with or without facial palsy.

(c) Presence of bilateral, unexplained hilar enlargement, with or without parenchymal pulmonary involvement.

(d) High or abnormal serum proteins.

(e) Repeated negative intracutaneous tuberculin reactions, at times at concentrations up to 10 milligrams.

(f) Absence of clinical and laboratory evidence of pulmonary tuberculosis.

SITES OF SARCOID LESIONS

The disease was found in almost every organ but the five commonest sites were, in order: lymph nodes (43 cases); lungs (28 cases); skin (23 cases); liver (20 cases); spleen (15 cases). (See Table V.) However, the incidence of organs involved is probably greater than the figures would indicate since they are based on demonstrable pathological or/and clinical findings only, and it is well established that sarcoid lesions may be present without any clinical evidence or even gross pathology. Moreover, many serial X-rays are often required to detect all bone lesions since they may supervene at any time, persist for indefinite periods, regress spontaneously, reappear at a later

TABLE IV

ANALYSIS OF SARCOID LESIONS FOUND INCIDENTALLY AT AUTOPSY

CAUSE OF DEATH	SITES OF SARCOID LESIONS	PULMONARY TUBERCULOSIS LESIONS
1. Diabetic coma	Mediastinal, aortic and mesenteric lymph nodes, spleen and lungs.	Not mentioned.
2. Subarachnoid haemorrhage.	Lungs.	Not mentioned.
3. Hypertension and cerebral haemorrhage.	Peribronchial, pyloric and aortic lymph nodes, liver, spleen and pericardium.	Not found.
4. Hypertensive disease.	Liver.	Not mentioned.
5. Tetralogy of Fallot.	Hilar nodes, lungs, liver and spleen.	Not found.
6. Meningioma and bronchopneumonia.	Lungs, liver and spleen.	Not found.
7. Chronic subdural haematoma.	Hilar nodes and lungs.	Not found.
8. Intestinal obstruction.	Liver and spleen.	Present.
9. Myocardial infarction.	Lungs.	Not found.
10. Strangulated hernia.	Lungs.	Not found.
11. Myocardial infarction; portal cirrhosis.	Hilar and thoracic lymph nodes, liver and lungs.	Not mentioned.
12. Meningococcal septicaemia; portal cirrhosis	Hilar nodes and spleen.	Not mentioned.
13. Seminoma of testis with metastases.	Mediastinal lymph nodes, lungs, liver and spleen.	Not mentioned.
14. Arteriosclerotic heart disease with failure.	Mediastinal and hilar nodes, lungs and liver.	Not mentioned.
15. End stage glomerulonephritis.	Mediastinal nodes, liver and spleen.	Not mentioned.
16. Carcinoma of right breast.	Regional axillary nodes.	Not found.
17. Collagen disease.	Brachial lymph nodes and lungs.	Not found.

TABLE V

SITES OF SARCOID LESIONS IN 75 CASES

ORGAN	NO. of CASES	NO. of PROVEN* CASES	NO. of UNPROVEN CASES
Lymph nodes.	43	37	6
Lungs.	28	23	5
Skin	23	21	2
Liver.	20	17	3
Spleen.	15	12	3
Eyes.	7	4	3
Parotid.	5	4	1
Nervous system.	4	2	2
Heart.	3	3	
Pancreas.	3	3	
Kidney.	2	2	
Bones.	4	4	
Tonsils.	2	2	
Miscellaneous.	4	4	
Totals	75	68	7

*As estimated by biopsy, at autopsy and by clinical findings.

date, and even be present without demonstrable radiological findings.

The commonest lymph node area involved was the hilar group (23 cases), usually bilateral. Single lymph node group involvement (24 cases) was a little more frequent than multiple group involvement (19 cases).

INCIDENCE OF LOCALIZED AND OF GENERALIZED SARCOID LESIONS

Boeck's sarcoid was found in one organ only in forty-one cases, and was demonstrated in two or more organs in thirty-four cases. (See Table VI.) The commonest sites of localized lesions were skin (20 cases) and lymph nodes (13 cases). However, most of these patients were examined once only and the subsequent course of the disease is not known. In the unproven group, all had generalized sarcoidosis.

CLINICAL MANIFESTATIONS

COMPLAINTS.—We have carefully investigated the incidence and nature of symptoms as observed by the patients

TABLE VI

INCIDENCE OF LOCALIZED AND MORE EXTENSIVE SARCOID LESIONS

NUMBER OF ORGANS INVOLVED	NO. of CASES	NO. of PROVEN CASES	NO. of UNPROVEN CASES
One organ only	41	41	0
Two organs	11	10	1
More than two organs	23	17	6
Total	75	68	7

themselves. (See Table VII.) Complaints were present in fifty-three cases —forty-six of which were proven pathologically, and absent in twenty-two cases. Like the disease, they concerned any organ or system but most frequently skin lesions (23 cases), constitutional symptoms (16 cases), respiratory symptoms (13 cases), painless lumps (12 cases) and neurological symptoms (7 cases). They were usually mild and disproportionate to the extent of the disease; even generalized sarcoidosis might be present with but few symptoms. Actually the presenting symptoms which brought the patient to the physician were constitutional in only six instances, respiratory in ten, ocular in three and neurological in two; seventeen came because of skin lesions, twelve because of painless lumps, one because of painful lump, and one because of jaundice. The lesions in such organs as lungs, liver, spleen, and in the central nervous system, were sometimes so extensive as to give rise to severe mechanical interference with function, leading to respiratory failure, cor pulmonale, portal hyper-

TABLE VII

INCIDENCE AND NATURE OF CLINICAL SYMPTOMS IN 53 CASES

SYMPTOMS		NO. of CASES
Constitutional:		*16*
	Fever	13
	Weakness	11
	Weight loss	11
	Malaise	5
Respiratory:		*13*
	Cough	11
	Sputum	9
	Shortness of breath	7
	Chest pain	3
	Wheezing	2
	Hoarseness	1
Neurological:		*7*
	Pain	2
	Paralysis	5
	Paraesthesia	2
Ocular:		*5*
	Photophobia	2
	Loss of vision	2
	Iritis	2
	Redness	1
	Soreness	1
	Lacrimations	1
	Exophthalmos	1
	Grittiness	1
Skin Lesions:		*23*
	Nodules	19
	Cysts	1
	Plaques	3
Painless Lump:		12
Painful Lump:		1
Jaundice:		1

tension, specific neurological pictures, etc.

Signs.—Generally speaking the clinical signs resulted from enlargement of organs, mechanical interference with function and, in some cases, from associated inflammation. This has been implied in the above comments; however, the following findings on physical examination may be noted:

(a) Skin lesions (23 cases)—either miliary and nodular sarcoids of Boeck, diffuse plaque-like lupus pernio of Besnier, or subcutaneous sarcoids of Darier and Roussy.

(b) Enlarged lymph nodes (22 cases)—non-tender, movable and small, usually under 1.5 cm.

(c) Palpable liver (12 cases) and spleen (11 cases)—both usually smooth, firm and moderately enlarged.

(d) Chest—in the absence of diffuse extensive involvement of the chest, respiratory signs were minimal or absent.

X-RAY FINDINGS

It was possible to study the chest X-ray findings in only thirty-four cases since, in many patients, the physician had apparently felt that there was no indication to have radiological examination of the chest. In thirty cases (88 per cent) the X-ray findings were abnormal. Bilateral hilar node enlargement was the commonest abnormality, reported in fifteen cases. The parenchymal findings were fairly evenly distributed between the following three types: linear striations, 7; nodular densities, 7; infiltrations, 5. Cavities or emphysematous blebs were found in one case only. It is understood that two or more of these findings may be associated in the same patient. In view of the limited number of cases in which it was possible to take serial roentgenograms, the course of the lesions can not be completely appreciated. However, definite regression of hilar masses and of pulmonary involvement was observed in some patients. Others showed progression, leading to death occasionally.

Bones.—X-rays of bones were reported in ten cases. Positive findings were seen in only four cases and involved hands and feet most commonly.

Other signs of the disease will be dealt with separately, because of their special interest.

SOME INTERESTING SYNDROMES

1. *Uveoparotid Syndrome.*—By this, we mean the presence of uveitis and enlargement of the parotid, usually bilateral, with or without enlargement of the submaxillary and submental salivary glands, low grade fever and peripheral type of facial palsy. This syndrome was present in five cases in this series.

2. *Orbital Tumour.*—One patient presented with pain along the fifth cranial nerve, exophthalmos and ptosis, suggesting cavernous aneurysm. Post-operative pathological examination revealed gross sarcoid involvement of orbit.

3. *Cauda Equina Tumour.*—One patient with proven sarcoidosis presented with symptoms and signs of a cauda equina tumour which was attributed to a sarcoid lesion.

4. *Obstructive Jaundice.*—One patient was admitted with symptoms and signs of obstructive jaundice; post-operative report revealed sarcoidosis of the head of the pancreas compressing the common duct.

5. *Portal Hypertension.*—A young woman presented with enlarged liver and spleen and portal hypertension, suggesting portal cirrhosis. A successful splenorenal anastomosis was done; pathological examination of the spleen and biopsy of the liver revealed extensive sarcoid.

6. *Multiple Cystic Bone Lesions.*—In one case, sarcoid involvement was found primarily in the bones of hands, feet and nose.

7. *Unsuspected Generalized Sarcoidosis.*—A thirty-one year old woman presented with fatigue and malaise which was attributed to a hypochromic anaemia following upon a menorrhagia. The patient died within six months from acute congestive heart failure. Post mortem examination showed sarcoid lesions in lungs, kidney, pancreas, lymph nodes, with diffuse extensive involvement of the heart. This case is an example of progressive sarcoidosis with no clinical findings to arouse suspicion of the correct diagnosis.

LABORATORY FINDINGS

Haematology. Haemoglobin and erythrocyte estimation were usually normal. The total leucocyte count varied between 1,600 and 14,700, the usual range being between 4,000 and 10,000 per millilitre. The extremes of percentage of lymphocytes were 7 and 26, the usual range being 10 to 16 per cent. In most patients examined, monocyte and eosinophile percentages were normal but in a few patients monocytosis (up to 14 per cent) and eosinophilia (up to 5 per cent) were recorded. The sedimentation rate (Westergren) varied between 2 and 150 millimeters per hour, in most cases being less than 40 millimeters per hour. In one-third of the patients with an elevated sedimentation rate, generalized sarcoidosis was the only disease found.

Serum Proteins. Serum proteins were estimated in twenty-four cases. Total protein levels varied between 5.9 grams per cent and 9.2 grams per cent; globulin fraction between 2.6 per cent and 5.0 per cent. High total protein (more than 8.0 grams per cent) occurred in eight cases; high globulin (more than 3.0 grams per cent) in eight cases also. Abnormal globulin, precipitating at 13½ per cent sodium sulphite, was found in ten cases, the extremes being 0.2 per cent and 2.6 grams per cent.

It is understood that one or more of these findings might occur in one patient.

Tuberculin Reaction. Intracutaneous tuberculin reaction was done in twenty cases and was negative in eleven, positive in six, and variable in three. By variable reaction is meant variable results at the same concentration at different times. The six patients with positive tuberculin reaction all had a definite history of contact with tuberculosis. Two proven cases of generalized sarcoidosis had, at some time, tubercle bacilli in their sputum; in these cases, the tuberculin reaction was positive in one and variable in the other, becoming positive at the same concentration after tubercle bacilli were found in the sputum.

COURSE AND PROGNOSIS

It was possible to follow the course of the disease in thirty-one cases; sixteen pursued a progressive course, the disease becoming more extensive or more severe. The progression was steady or intermittent and usually prolonged over several years. However, one patient died within six months of the onset of symptoms. From the information available over a limited period of time, the remaining

fifteen patients appeared to be stationary or regressive. Regressive findings were observed most frequently in lungs, lymph nodes and skin.

In the progress of the disease, the structure and function of different organs and systems were often grossly altered. Patients with pulmonary disease suffered acute respiratory illnesses, often considered bronchopneumonia, which were resistant to antibiotic treatment; pulmonary fibrosis and emphysema developed in others, as did bronchiectasis. Cor pulmonale and portal hypertension each developed in one instance. One patient became blind. Active pulmonary tuberculosis supervened in two cases.

Fatal Cases. It is believed that sarcoidosis was the cause of death in five cases in this series. They died within six months to five years of the onset of symptoms. All these fatal cases had generalized sarcoidosis; four of them had severe involvement of the lungs; in the other case, as mentioned above, the diagnosis was not suspected until generalized sarcoidosis with extensive involvement of the heart was demonstrated at autopsy.

TREATMENT

Because of the natural tendency of the disease to undergo spontaneous remissions, any form of treatment was difficult to evaluate. In this survey, the administration of arsenic, calciferol and roentgen radiation was not attended by significant improvement. Urethane was used in one patient with apparent beneficial results.

In localized cases, adequate surgical excision of the lesion was followed by uneventful healing and, as far as was known, these patients did not subsequently report with evidence of the disease.

The nitrogen mustards, cortisone and ACTH were not used in this series of cases.

SUMMARY AND CONCLUSIONS

There were seventy* cases of Boeck's sarcoid among over 300,000 admissions to the Toronto General Hospital between the years 1938 and 1950. The incidence was increasing from year to year, however, which probably indicates an increasing professional awareness of the disease. The sexes were affected almost equally, and the disease was most common after the age of forty years. Pathological demonstration of diagnosis was obtained by biopsy or at autopsy in 91 per cent of the cases; in the remainder the diagnosis was based on reliable clinical criteria. Sarcoidosis was the cause of the patients' symptoms in fifty-three cases; in twenty-two cases, it was incidental to a heterogenous group of diseases. It is noteworthy that, in five of the latter group, localized sarcoidosis was found in lymph nodes regional to primary carcinoma.

The organs most commonly involved were, in order, lymph nodes, lungs, skin, liver and spleen; lymph node involvement most frequently occurred in the hilar and axillary regions. The disease was localized in about half the cases, and involvement of skin and of lymph nodes accounted for 80 per cent of the localized cases. The patient complained of symptoms due to sarcoidosis in 71 per cent of cases; the commonest complaints were, in order, skin lesions, constitutional reactions, respiratory symptoms, and the presence of a painless lump. There was

*Records of five cases not admitted to hospital, in which diagnosis was made by biopsy in the Department of Pathology, were also studied.

little correlation between the extent of the disease and the severity of the symptoms. Some patients with minimal symptoms had quite extensive disease. In others, the function of an organ became seriously impaired by the mechanical interference of an extensive lesion, e.g.: obstructive jaundice, portal hypertension, cor pulmonale, etc.

Discrete lymphadenopathy, skin lesions, moderate hepatomegaly and splenomegaly, and bilateral abnormal chest X-ray findings were the most prominent signs of the disease. Repeated chest roentgenograms were helpful in diagnosing and following the course of the disease. No specific haematological findings were observed, but high or abnormal serum proteins and negative tuberculin reaction frequently supported the diagnosis. All six patients with positive tuberculin reactions had a definite history of contact with tuberculosis, and the two patients in which active pulmonary tuberculosis supervened had positive tuberculin reactions also.

The disease pursued a variable, erratic and unpredictable course, extending progressively or intermittently in many cases, but remaining stationary or regressing in others. Moreover, some patients showed local regression with simultaneous extension elsewhere. A more serious prognosis was suggested in generalized sarcoidosis, particularly when the lungs were extensively involved. Though the course was usually benign, it is noteworthy that five patients with generalized sarcoidosis died from the disease.

As regards treatment, surgical excision of the lesions appeared to be effective in localized cases. The treatment of generalized sarcoidosis was less satisfactory but beneficial results were achieved by administration of urethane in one patient.

Finally, it is suggested that complete investigation and regular follow-up of patients with any form of sarcoidosis would help to elucidate many still unsolved problems of aetiology, pathogenesis, prognosis and management of this strange disease.

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SPECIAL INTERNESHIP

Arrangements are being made for special internships designed to prepare doctors for general practice. These internships will be limited to three in number for the hospital year beginning July 1st, 1952.

The program includes four months in Paediatrics at the Hospital for Sick Children, four months in Obstetrics and Gynaecology at the Toronto General Hospital and four months in Medicine at the Toronto General Hospital, Wellesley Division.

These internships are being offered to doctors who have completed at least one year on a rotation internship. Application should be made immediately to Dr. R. C. Dickson, Wellesley Hospital, Homewood Place, Toronto 5.

RETROLENTAL FIBROPLASIA

J. G. EVANS AND J. R. EVANS, 5T2

INTRODUCTION

The chances of survival of the premature infant improve each year as medical ingenuity combats the disadvantages of too early acquisition of an independent environment. In the last decade an additional hazard to the premature infant has been recognized which, because of its increasing incidence and grave prognosis, demands our consideration.

In 1942 Dr. Theodore L. Terry first noted the relationship between prematurity of birth and the development of opacities behind the lens in infants' eyes. He described an opaque vascularised membrane forming after birth due to the functional persistence of embryonic intraocular blood vessels beyond their normal time of involution. To this condition he gave the name Retrolental Fibroplasia. He assumed that the hyaloid artery, a vessel traversing the vitreous from the optic disc to the lens, and the tunica vasculosa lentis, a vascular network surrounding the lens, provided a nucleus for the proliferation of connective tissue and for the formation of a mass in the vitreous chamber of the eye. Although Terry's explanation of the pathogenesis of this condition has not been born out by subsequent investigation, his original observations of this intraocular pathology as a clinical entity, developing after birth in association with prematurity, account for the persistence of the name with which he labelled the disease.

PATHOLOGY

The syndrome which Terry described was in reality the end stage of the pathological process. Owens and Owens subsequently demonstrated from clinical and pathological examination of the eyes of premature infants that Retrolental Fibroplasia was primarily a disease of the retina and in no way related to the hyaloid system as Terry had originally proposed. In nearly all cases involution of the hyaloid artery and tunica vasculosa lentis was found to be complete prior to the first recognizable manifestations of the disease. They attributed the condition to progressive vascular changes originating in the retina and subsequently involving the other contents of the posterior chamber of the eye.

Microscopic study has established the sequence of events in the early stages of this disease. The lesion originates in the inner nerve layer of the retina where proliferation of the capillary endothelium and secondary glial response occurs. With growth this angiomatous tissue ruptures the internal limiting membrane and spreads along the surface of the retina as well as into the substance of the vitreous. The mechanics of blood flow are so altered by the structural changes in the vascular bed that localized edema formation and occasional hæmorrhages occur. As the edema becomes more generalized elevation of the swollen retina is apparent peripherally. The retinal folds are raised by an in-

creasing volume of exudate and tend to become adherent to one another forming a retrolental membrane which maintains its attachment to the ciliary body and the optic disc. Behind the membrane endothelial and glial proliferation transform the vitreous body into a disorganized solid mass. Further accumulations of chorioretinal exudate and hæmorrhage displace the lens and iris forward permitting adhesions to form between the lens and adjacent structures.

CLINICAL MANIFESTATIONS

Fundoscopic examination reveals clinical stages which closely parallel the pathological process in Retrolental Fibroplasia. The initial manifestations are visualized between the third and ninth week after birth. The first change is an increase in the number of vessels at the periphery of the fundus. The retinal veins become dilated two to four times their normal size and the arteries display corresponding enlargement and marked tortuosity. Although this neovascularization of the retina is the first recognizable stage of the disease, inconstant earlier observations are reported by other investigators. Locke, Owens, and LaMotte, have noted constriction and attenuation of the retinal vessels in over 30% of these infants but in some no further progress has occurred. Guy has reported cloudiness of the vitreous as early as the second week of life with subsequent retinal changes in a statistically significant percentage of his series.

The second stage of the disease is the phase of retinal involvement. The periphery of the fundus reveals patchy grey elevated areas while small hæmorrhages and vitreous haze may also be evident. As the retina becomes diffusely edematous, prominent elevations testify to its detachment. As a rule these changes are restricted to the circumference of the fundus; however in some instances the process is initiated at the posterior pole.

The stage of membrane formation is the final phase of the disease. As the elevated retinal folds become adherent the result is visualized as partial or complete occlusion of the pupil by a greyish-white vascular membrane behind the lens. Rarely do both eyes reach this stage simultaneously despite the bilateral nature of the disease. The acute pathological process is usually completed before the sixth month, although exacerbations have been recognized as late as the fourth year.

With the acute phase over, the atrophic retina undergoes cicatrization and, due to the persistent attachment to the ciliary body, dentations appear like the teeth of a comb when looking as obliquely as possible at the lens. In long standing cases the eyes are small and sunken, the anterior chamber shallow, the iris atrophic and fœtal blue in colour, and the lens fixed by anterior and posterior synechiæ. Glaucoma may result in cases where the filtration angle is markedly narrowed by anterior displacement of the iris. A searching nystagmus is often present. The eyes are blind in this far advanced state although light perception may be present.

When the developmental sequence of this disease is followed, the diagnosis presents little difficulty. However the terminal or membranous stage of Retrolental Fibroplasia must be differentiated from several other conditions. Retinoblastoma may present as a yellowish retrolental mass but it is usually unilateral and not associated with other evidence of ocular disease. Pseudoglioma appears in children over the age of two

following, in most cases, a severe generalized infection. Remnants of the embryonic intraocular vascular system may simulate Retrolental Fibroplasia but this condition is present at birth and involves only one eye usually.

INCIDENCE

Although Retrolental Fibroplasia was not recognized as a clinical entity until 1942, there can be no doubt that it existed before that time. However the recent increase in frequency cannot be explained as previous failure to recognize the disease because the number of cases discovered since 1942 far exceeds the number of cases of blindness which could possibly have been due to this condition. Even during the last decade a significant progressive increase in the number of cases has been noted by the same investigators.

The incidence of this disease maintains one fairly constant relationship, being inversely proportional to the birth weight of the infant. It is very rarely seen in term infants, the vast majority of the cases occurring in infants under four pounds. Owens and Owens in Baltimore report evidence of Retrolental Fibroplasia in 7% of infants under 4½ lb., and in 50% of infants under 3 lb. From Birmingham, England, Dr. Mary Cross lists corresponding figures: 0.1% of all prematures; 0.8% of babies under 4 lb.; 4.2% of babies under 3 lb.

The geographic distribution of the disease is particularly unusual. It is most common in the United States but varies unbelievably from one city to another or even from one hospital to another in the same city, where for all intents and purposes, the premature infants are subjected to the same influences. The disease is chiefly restricted to larger centres and cases in rural areas are rare. As exemplified by the figures of Dr. Cross in Great Britain, this condition is much less frequent in Canada and most European countries. Lack of personnel experienced in the recognition of the early stages may account for some of the difference but certainly not all. The Toronto Hospital for Sick Children rarely sees more than five or six cases of Retrolental Fibroplasia in the course of a year, whereas in corresponding hospitals in New York or Boston, from 30% to 70% of the infants on the premature service at any one time would show evidence of this pathological process. Over half of such cases undergo complete and spontaneous remission so careful repeated examinations are required for their detection.

The occurrence of this disease varies greatly from year to year even in the same geographic location. Recently at Hartford the incidence was reduced by half without any form of therapy and for a period of nine months no cases were seen. This factor in particular makes statistical studies unsatisfactory because no standards or control series are reliable. The unpredictable aspects of the incidence of this disease account for much of the delay in its investigation.

ETIOLOGY

When birth occurs at six to seven months gestation, the eye is undergoing both constructive and retrogressive changes. This unstable ocular system provides the setting in which Retrolental Fibroplasia is manifested but the significance of the developmental changes in the pathogenesis of the disease is as yet undetermined. The growth of the eye after birth is exceedingly rapid. It is postulated that a disturbance, prob-

ably metabolic in origin, might derange the synchronous development of the vascular system of the retina and choroid. If dilatation and tortuosity of the veins is produced artificially, the resulting sequence of vascular stasis, diffuse exudate formation, hæmorrhage, and patchy elevation of the retina, closely parallels the clinical observations in the early stages of Retrolental Fibroplasia. However the factor initiating these vascular changes still remains a mystery. Many etiological agents have been suspected during the short history of the disease but in spite of vigorous investigation, no absolute relationships have been proven.

Most attention has been directed to the period of care of the baby after birth. Kinsey and Zacharias at the Boston Lying-In Hospital noted a direct correlation between the rise in incidence of Retrolental Fibroplasia and the increase in amount of water soluble vitamins administered to premature infants over the period from 1943 to 1947. Excessive absorption of Vitamin A was incriminated as the etiological factor. However in a subsequent two year study, the incidence was not significantly altered by the omission of both Vitamin A and Vitamin B.

Similarly in 1946 Krause was unable to explain a sudden dramatic rise in the incidence of Retrolental Fibroplasia to six times that of preceding years, in infants under 3½ lb. weight. The only factor with which he could correlate this increase was the use of a new multivitamin preparation containing propylene glycol as a dispersing agent. After substituting a homogenized preparation with identical vitamin content the incidence returned to the normally expected level suggesting that the emulsifying agent was the toxic factor. Subsequent observations by Kinsey, Zacharias, and Krause, have exonerated the dispersing agents from any etiological role.

However vitamins were not entirely dropped from the focus of attention. In 1949 Owens and Owens proposed that Vitamin E deficiency might be responsible for the ocular pathology. This assumption was based on the work of Menschik and his co-workers who observed in experimental animals that this vitamin had a significant role in fat metabolism. In premature infants the low fat diet and inefficient fat metabolism reduce the available quantity of the vitamin and this deficiency in turn is accentuated by the high intake of Vitamin A which increases the demand for Vitamin E within the organism. Therapeutic trials were conducted using dl-alpha-tocopherol acetate as the source of vitamin E. Although nearly half of the subjects in each series displayed some early manifestations of the acute disease, no correlation could be established with initial blood levels of the vitamin. However in Boston the incidence of residual Retrolental Fibroplasia dropped from 20% to 5%, while in Baltimore Owens and Owens noted that the percentage of cases with membrane formation was reduced from 22% to 8%. Both Kinsey and the Owens concluded that Vitamin E administration did not alter the incidence of early retinal changes but that, when given prophylactically, it appeared to reduce significantly the percentage of cases with severe residual intraocular pathology. Both groups of investigators were reticent to attach great significance to the role of Vitamin E because of the spontaneous tendency to regression associated with this disease and further unpublished work of the Owens tends to repudiate the view that the pharmaco-

logical action of Vitamin E is of value in this condition.

The nature of the feeding given to premature infants has been regarded as an important factor in the development of Retrolental Fibroplasia. In Sweden the remarkably low incidence of the disease is attributed to the widespread use of breast milk. Up until 1951, only five cases were reported and all of these were in children fed on cow's milk. Dr. Alan Brown also places the blame for this disease on artificial feeding. However, in New Orleans where Retrolental Fibroplasia is relatively common, the premature service of one hospital has a negligible incidence of the disease despite artificial feeding.

Thus far, little has been discovered to suggest that Retrolental Fibroplasia is of inflammatory origin but Boran of Paris is convinced that we are dealing with a disease of virus etiology. This opinion is particularly consistent with the widespread geographic variations and yearly fluctuations in the incidence of the disease. The unexplained presence of inflammatory cells in the choroid of about 15% of Locke's series of cases also tends to support this view. However, egg embryo inoculations of intraocular contents have been non-productive.

Up to the present time research has been directed at isolating some aspect of the post-natal care of the premature baby as the cause of this disease. As the earliest manifestations of the pathological process are observed closer and closer to the time of birth, it seems reasonable that increasing etiological responsibility must be shouldered by factors acting during pregnancy and parturition. Already maternal age, parity, Rh type, multiplicity of birth, disease and therapy during pregnancy, and many other factors in the prenatal period have been searched for some relationship. In addition the cause of prematurity, type of delivery, obstetrical anaesthesia and analgesia, and foetal anoxia have been scrutinized but no statistically significant correlation has emerged. However, Ingalls maintains that more intricate statistical analysis is indicated especially with respect to those factors which might result in foetal anoxia. With animal experiments he has demonstrated that anoxia is a teratogenic agent. By exposing the maternal organism to a low oxygen environment at different stages of gestation he has produced a wide variety of congenital defects consistent with the time of exposure. In mice, anoxia on the sixteenth day produces the open eye defect which is not unrelated to Retrolental Fibroplasia. Warkany has obtained similar congenital anomalies with a parallel gestational time relationship by employing riboflavin deficient diets. Lack of this vitamin results in polycythemia in the experimental animal suggesting that anoxia may be the mechanism of action through which riboflavin deficiency acts. The importance of anoxia in the pathogenesis of Retrolental Fibroplasia is difficult to assess but Ingalls pleads for closer investigation of maternal systemic irregularities and placental disorders liable to result in its production.

MANAGEMENT

Although the investigations of Retrolental Fibroplasia have revealed few concrete measures which may be employed therapeutically, they have demonstrated fairly conclusively that the present methods of care of premature infants are not the offending factors.

The role of ACTH and Cortisone in

this disease are under intensive study at the present time. Treatment is based on the premise that hyperadrenalism exists in the last trimester of pregnancy. In the premature infant, early removal from the endocrine influence may permit the angiomatous endothelial proliferation since it is accepted that hyperadrenalism retards the development of mesenchymal cells and that cortisone specifically inhibits capillary growth.

Reese and Blodi in New York administered daily doses of 20 to 25 mg. of ACTH for fourteen days to premature infants showing early progressive retinal edema or retinal elevation. Their results may be summarized as follows:

TABLE 1

	Treated	*Untreated*
No. of Eyes	34	14
Good Results	25	4
Poor Results	4	10
In Between	5	0

The percentage of residual blindness was reduced to less than one quarter of the figures previously reported (8% - 11%). However, because the control series was inadequate, and the number of cases so small, no conclusions may be drawn from these results as to the effectiveness of this form of therapy. Subsequent small series with adrenal hormones have produced slightly less optimistic results.

The limitations of ACTH and Cortisone therapy must be recognized.

1. Their use imposes systemic hazards on the premature infant which is associated with a high mortality rate (15%). The infant fails to gain weight despite a voracious appetite and a high caloric diet. The susceptibility to infections is increased greatly and the response of the host is unrecognizable. For this reason prophylactic Aureomycin is routinely administered. Severe shocking diarrhea was observed in over 50% of one series receiving Cortisone. In general most of the sequelae may be avoided by limitation of therapy to a maximum of three weeks.

2. The hormones are effective in preventing further progression of the pathological process and in causing prompt retrogression of reversible retinal changes such as edema and partial detachment. However, they have no use once retinal separation is complete or mass formation is underway. In addition they will not bring about disappearance of the angiomatous proliferations already in attendance at the onset of treatment.

3. Since the duration of therapy is limited to three weeks, treatment must not be initiated until progressive retinopathy is evident. Earlier commencement of treatment offers no improvement in results and increases the incidence of sequelae.

The therapeutic value of Vitamin E has been discussed and at the present time holds little favour.

SIGNIFICANCE

In spite of the low incidence of Retrolental Fibroplasia in Canada at the present time, the prevalence of this condition in the United States compels us to make routine ophthalmological examinations at regular intervals on all premature infants, especially in the dangerous weight group. The fact that this disease is responsible for nearly one half of all blindness in young children in the United States should supply the necessary incentive.

ACKNOWLEDGEMENT

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INTRAVENOUS

It takes a wizard or a gen'us
To find a vein for intravenous!

* * *

Enters the Doc. (Professionally)
An interne with a tournquet.
He ties it, saying "Close your hand."
He waits to see the vein expand.
He gives the arm a gentle twist,
And fumbles lightly near the wrist,
And says "I think we'll try it here!"
With needle set he makes a spear.
The vein side steps, and oh, alas!
He has to make a second pass.
This time a higher spot he'll choose.
Another stab—another bruise.
But hopeful still, the man in white
Commands the patient—"Close it tight!"
Three times and out—still there's no harm—
The patient has another arm!

(With chin set firm and steady tread,
The doctor walks around the bed.)

Once more the rubber band he ties.
And seeks a vein with searching eyes.
"We'll find one now", he sighs, "or bust"
Anon—he takes a vicious thrust.
Distressed he pierces, stabs and spears
(The patient is reduced to tears).
Then trying hard to hide his shame
He talks about the rugby game.
(That touchdown was as nice a play
As Doc had seen for many a day!)
And as he talks he tries again—
And accidently strikes a vein.
And when there flows life-giving fluid,
The patient asks "How did you do it?"
"Have veins no stationary course,
That you could trace them to their source?
Does study of phlebology
Not aid the man with tourniquet?"

* * *

May heaven send us men of science
Who show some skill with this appliance!

(Being a play by play report by the patient.)

M. J. Scott (Epistaxis '38)

CLINICAL PATHOLOGICAL CONFERENCE*

THE HOSPITAL FOR SICK CHILDREN, TORONTO

PRESENTATION OF CASE (*Dr. Alice Goodfellow*):[1]

The case is that of D.D., a two and a half years old male infant who was admitted with the following complaints:

Persistent cold for two months.

Flu for one week.

Fever, chills, and drowsiness for 10 hours.

Hemorrhagic rash for five hours.

Family history: one sibling had the flu at the same time as this child.

Personal history: patient had tonsillectomy four weeks before admission.

History of present illness: Patient was in his usual state of good health until two months before admission, at which time he developed a cold. The cold lingered on despite treatment with sulfa drugs, nose drops, and nightly chest rubs. One week before admission the cold became more severe and the family regarded this as the flu. Twelve hours before admission the child became very restless and feverish. Five hours before admission he became drowsy and developed a rash which became very marked over the ensuing five hours until the time of admission.

On examination: The child appeared well developed and well nourished, and was almost moribund. There was a hemorrhagic rash over the entire body. His eyes were glazed. The pharynx was very red and covered with an exudate; there were petechial spots on the buccal mucosa.

Investigations: A lumbar puncture was done, and the cerebrospinal fluid showed four cells per cu. mm. The white blood count was 28,800; the hemoglobin, nine grams. The blood culture grew meningococci, as did the cerebrospinal fluid.

Treatment: The patient received intravenous fluids and transfusion, and Aqueous Penicillin intramuscularly every four hours. In addition, 10 cc. of adrenal cortical extract was given intravenously on admission, followed by five cc. of adrenal cortical extract every four hours intramuscularly. Cortisone was also given intramuscularly, 25 mgm. initially, and 12½ mgm. every four hours. Three additional doses of 12½ mgm. were given by stomach tube.

Course: During the first twenty-four hours, the child progressed moderately well although hemorrhagic areas were more severe and generalized. About twenty-eight hours after admission the child's respirations became gasping and irregular. The temperature rose to 106 degrees, and he died suddenly.

Final clinical diagnosis: Meningococcemia.

POST MORTEM FINDINGS (*Dr. W. Cochrane*):[2]

The body was that of a well nourished male infant with petechial hemorrhages chiefly over the nose and left leg. The trachea, larnyx, and bronchi were filled with a large amount of pus, and the mucosa was denuded and reddened. The lungs weighed 190 grams (normal: 85). Petechiæ were present on the pleural surfaces. The upper lobes were feathery in consistency, while there were de-

*April 6, 1951.

[1]Senior Interne in Pediatrics.

[2]Interne in Pathology.

pressed firm blue areas in the lower lobes.

The heart weighed 109 grams (Normal for this age: 60). It was uniformly enlarged with a thin flabby ventricle. The liver was enlarged, yellowish, and brownish in colour, and weighed 609 grams, the average normal for this age being 418 grams. The spleen was enlarged, twice the normal weight of 36 grams, very firm, and purplish with pale, greyish-white, confluent, mottled areas over the surface.

The kidneys weighed 90 grams (normal: 49 grams for this age). They were swollen, with a dark purple surface. The cut surface revealed reddish zones under the capsule and between the cortex and medulla. The medulla showed increased vascular streakings. The adrenals were normal.

The brain was edematous with congested vessels over the hemispheres, and a slight amount of yellowish purulent material along the perivascular spaces and over the occipital cortex. There were no meningococci cultured from the trachea, lungs, or brain at necropsy.

MICROSCOPIC FINDINGS (*Dr. W. L. Donohue*):[3]

Sections of the lung showed extensive bronchopneumonia. Those of the brain revealed early meningitis.

The usual finding in such a fulminating case of meningococcemia is a Waterhouse Friderichsen syndrome with massive hemorrhages into the adrenals. In this case, however, the interesting findings are in the kidneys. There are hemorrhagic areas just below a narrow band of viable tissue below the capsule. Then there is a wide band of completely necrotic tissue and again a slight narrow viable band between cortex and medulla; there is almost complete necrosis of cortical tissue. On examination of the interlobar arteries they were found to contain cellular masses in which no bacteria were found. The cells, however, were not definitely identified. The walls of the arteries were swollen and edematous with fibrinoid degeneration of the endothelial cells. The cellular masses were considered to be sloughed endothelial cells of the blood vessels impacted in their lumina. This is a case of symmetrical necrosis of kidney cortex.

Approximately two thirds of such cases occur in pregnancy, and the remainder in other conditions. Some of these conditions include severe toxemias, and serious infections. It has been suggested that the necrosis is due to the interruption of the blood supply at the level of the arcuate arteries causing ischemia and necrosis of the kidney cortex. Trueta postulates that there may be a shunt of blood from the cortex through the juxta-medullary glomeruli, thus causing the ischemia of the major portion of the cortex.

Anatomical diagnosis:

(1) Meningococcemia
(2) Meningococcal meningitis
(3) Bilateral cortical necrosis of the kidneys.

DISCUSSION

Dr. Silverthorne:[4] I will present some of the history of this disease meningococcemia. This was a recognized disease long before the bacteriology was known or the art of lumbar puncture developed. In 1805 the earliest clinical report of this disease was given, and in 1806 a pathological report and description of the lesions appeared. The earliest report

[3] Pathologist.

[4] Physician, Hospital for Sick Children.

of a meningococcal epidemic in North America was in 1811. In 1887 the meningococcus was discovered.

Gordon at St. Bartholomew's, during World War I, divided the meningococcus into types I to IV. Branum grouped these types and in group I he placed groups I and III. Usually epidemics are due to the group I meningococci.

This disease usually starts as an upper respiratory infection and often adults in the homes of children who have the disease have the same type of meningococcus in their upper respiratory passages. There is some argument as to whether or not the disease extends through the cribiform plate to cause meningitis but it is questionable whether it is spread by this method. The French believed at one time that the disease was caused by swallowing the meningococci which were then absorbed through the gastro-intestinal tract. That this disease is essentially a bacteremia with a secondary meningitis is established by these four facts: First, the clinical appearance of the rash. Second, the smears of the skin lesions show the meningococci. Third, the cerebrospinal fluid may be sterile on the first day and the blood culture positive on that day. On the following day the blood culture may be negative and the cerebrospinal fluid positive. Fourth, early cases may have a ventriculitis before the meningitis, suggesting that the organisms get into the ventricles *via* the choroid plexus. The present case illustrates the metastatic lesions that can occur in the acute phase of this disease. It also suggests that the meningococci are rapidly killed in the blood and tissues by an immune reaction. The patients who die in an acute meningococcemia usually die from an overwhelming toxemia or with a Waterhouse-Friderichsen syndrome.

Dr. A. L. Chute:[5] I have never seen such a case before. Death in this type of case can be caused first, by massive bacterial invasion, second, by toxemia, and third, by adrenal involvement. When there is adrenal involvement, the adrenal insufficiency must be replaced, first by adrenal cortical extract, large amounts of which are necessary, and secondly by cortisone. ACTH is of no use if the cortex has been knocked out by hemorrhage.

Trueta has shown that there is a relatively long passage in the cortical glomeruli from the afferent to the efferent arterioles. Through the glomeruli near the medulla, the so-called juxtamedullary glomeruli, there is almost a direct route from the afferent to the efferent arterioles, so that the blood filtration is much faster in these glomeruli than in the cortical ones. The afferent arterioles in the ordinary cortical glomeruli are greater in diameter than the efferent vessels; the afferent and efferent vessels of the juxta-medullary glomeruli are of the same diameter. Trueta has shown that with shock there is spasm of these vessels, and shunting of blood from the cortical to the juxtamedullary glomeruli so that the tubules become ischemic, and necrosis occurs. Trueta produced lesions similar to those seen today by the injection of staphylococcus toxin into a rat or rabbit followed by an injection of India Ink. The Ink was taken up by all tissues except the necrotic cortical tissue present in the kidney.

Dr. T. E. Roy:[6] The necrotic lesions seen in meningococcemia especially in necrotizing skin lesions may be caused by the so-called Schwartzman reaction. This

[5]Physician-in-chief, Hospital for Sick Children.

[6]Bacteriologist, Hospital for Sick Children.

is a peculiar type of reaction and has been discussed in the March 1951 issue of the Journal of Pediatrics. The preparatory substance is injected intracutaneously and one waits 48 hours. A provocative injection is then given intravenously and 24 hours later one sees a necrotizing reaction at the site of the preparatory injection, apparently due to the damage to the vessels. Bacterial filtrates elicit this reaction to the best advantage but are not necessary because killed suspensions of the bacteria have also been used.

This reaction is not due to a direct toxic effect; it is not an anaphylactic or allergic reaction, and it is not an immunity type of reaction since it lacks specificity. The provocative injection does not have to be antigenic, intravenous starch, for example, being able to produce the reaction. If the preparatory injection is introduced into a lymph node, one may get necrotizing lesions in the node.

The way in which the Shwartzman reaction will occur in meningococcemia is as follows: During the early bacteremia, meningococci are deposited in various tissues, which may be regarded as the preparatory injection. Later, a heavy bacteremia acts as the provocative stimulation, and the necrotic lesions occur at the sites of bacterial deposition. There is still some doubt as to whether or not this is a true explanation. Bilateral cortical necrosis in the kidney has been produced experimentally by the Shwartzman phenomenon.

ANSWERS TO "WHAT IS YOUR DIAGNOSIS, DOCTOR?" (Page 93)

1. Actinomycosis
2. Colles fracture
3. Intussusception
4. Chronic passive congestion
5. Tuberculous tenosynovitis
6. Yellow Fever
7. Cerebral spastic diplegia
8. Carcinoma (diffuse infiltrating)
9. Granuloma inguinale
10. Congenital syphilis
11. Portal cirrhosis
12. Cholera
13. Malignant nephrosclerosis or embolic glomerulonephritis
14. Ewing's tumour
15. Erb's paralysis
16. Tetanus
17. Marie-Strümpel spondylitis
18. Amyloid disease
19. Congenital syphilis
20. Disseminated lupus

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EDITORIALS

LOOKING BACKWARD

ANOTHER YEAR is fast drawing to a close. Already statisticians are describing the increases in population and department store sales, steel production and military budgets, that marked 1951. It was a year of *progress,* they solemnly assert, and to this we nod automatically in agreement, for "progress" is the main catchword of our time; to deny it is virtually to deny our birthright.

But was 1951 a year of progress? While all sorts of records were established in the production of television sets, plastic dolls, and atom bombs, a nadir was reached in the relation of man to his brethren. In the international scene mankind forgot the meaning of *fairness, understanding, compromise,* and *moderation,* and developed to a fine degree the postulate that "might is right". The cleavage of the world into two camps became a *fait accompli,* and the greatest global unrest ever known to humanity became established.

The decline of international virtue had its counterpart in national scenes. In the United States of America, a new brand of slander that presumed a man guilty until absolutely proven otherwise was evolved, and named McCarthyism. In the South American Republic of Argentina, a dictator re-enacted history by destroying the free newspapers that opposed him; the beacon of truth of La Prensa was extinguished, and its pages now spew forth the lies of the Peronista. And in the Middle East, ambitious and greedy men, playing upon the ill-defined, but newly awakened, nationalism of the masses, stirred up national and interna-

tional animosity that may have terrible repercussions.

So went 1951. Whatever material progress was made was more than counterbalanced by the declining morals of humanity. There can be little regret in the passage into history of this relatively brief epoch. We can only hope that somehow the trend will be reversed in the coming year, and that man will regain some of the virtues he has lost. May nineteen hundred and fifty-two truly be a Happy New Year!

A CAUSE FOR CONCERN

Twenty-nine years ago, this Journal was founded to serve as an instrument of student expression, and to bring to students recent articles of scientific interest. It has long been my belief that the former purpose is the more important, for this is one of the few opportunities that a medical undergraduate has to prepare a scientific paper that has the clarity, detail, yet brevity, demanded of a published article. Indeed, the Journal provides an excellent proving ground for Bacon's aphorism: "Writing maketh an exact man".

Unfortunately the students at this medical school have not been availing themselves of this invaluable opportunity, and this tendency has become more marked in the post-war years. As the enrollment in the faculty has mounted, there has been a concomitant drop in student participation. This phenomenon has been of no little concern to my predecessors and myself.

Why are the undergraduates abstaining from writing? Many answers have been given to this query, most of them by people who have never written, or attempted to write, an article. Some contend that students have not sufficient experience to write scientific papers, and should restrict their efforts to general topics, such as the history of Medicine, which they can extract from books or other periodicals. I disagree with this view because I believe that students, while they lack the clinical experience of graduates, can still see, in the public wards of Toronto hospitals many examples of the conditions they wish to describe, and then do an adequate review of the literature.

Another explanation for the lack of student activity in the Journal is that the undergraduates are too concerned about their studies and quizzes. Certainly, the examination two weeks hence is of greater anxiety than any Journal deadline can ever be; on the other hand, if the students are persistently concerned only about their immediate affairs, their lack of foresight will eventually take its toll when they find that they are unable to describe original work in a form acceptable for publication.

This is now a time of concern for the welfare of the Journal. It can be resolved only by the concerted efforts of the medical undergraduates of this University who must earnestly seek to make the University of Toronto Medical Journal the real medium of student expression envisioned by its founders twenty-nine years ago.

Season's Greetings

The members of the Staff of the University of Toronto Medical Journal wish all its readers and advertisers a joyous festive season. May Christmas and the New Year bring the optimum in happiness and contentment to all.

HUMANISM AND MEDICINE

H. B. VAN WYCK*

PART XIX

EDWARD JENNER

THE LAST YEARS of the 18th century witnessed one of the supreme achievements of modern medicine—the successful establishment of preventive inoculation. This was the accomplishment of a country doctor who spent his life in the picturesque village of Berkeley, Gloucestershire.

There had been others in the field. Human inoculation of variolous virus was known long ago to most Oriental peoples. Mention of it appears in the "Flos" of the Medical School of Salerno. The idea was communicated to the Royal Society in 1713 by Timoni who described inoculation as he had seen it practised in Constantinople. To Lady Mary Wortley Montague belongs the honor of having been the first to bring inoculation to the western world. As wife of the English Ambassador, she had observed the practice in Turkey. In a letter from Adrianople dated 1717, she wrote: "Every year, thousands undergo this operation; and the French ambassador says pleasantly, that they take the smallpox here by way of diversion as they take the waters in other countries. There is no example of anyone who has died of it, and you may believe I am very well satisfied of the safety of the experiment since I intend to try it on my dear little son. I am patriot enough to take pains to bring this useful invention into fashion in England." Lady Mary had her three-year-old son inoculated in Turkey and her five-year-old daughter was inoculated on her return to England in 1721. It was because of the social prestige and forceful personality of this remarkable woman that her example made preventive inoculation from smallpox patients a relatively common practice in Europe and America before Jenner's time.

In one of the famous collection of Montague letters, Lady Mary writes: "Lady Byng has inoculated both her children, and is big with child herself; the operation is not yet over, but I believe they will do very well. Since that experiment has not yet had any ill effects, the whole town is doing the same thing and I am so much pulled about and solicited to visit people, that I am forced to run into the country to hide myself."

That the practice spread rapidly in spite of the considerable mortality from the inoculation itself attests the horror with which smallpox was viewed by the people of the time. John Baron, a Fellow of the Royal Society and the author of the classic "Life of Edward Jenner", wrote in 1838:

"From authentic and accurate calculations it has been ascertained that one in fourteen, of all that were born, died of smallpox. This was the calculation even after inoculation had been intro-

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duced. Of persons of all ages, in the natural way, one in five or six died, whilst of those who had been inoculated one only in fifty died. These conclusions were drawn by Dr. Jurin from an examination of the London bills of mortality for a period of forty-two years."[1]

The methods of variolation, as inoculation from smallpox patients was called, improved gradually during the 18th century. Robert Sutton with his two sons, Robert and Daniel, opened an Inoculation Centre in Essex. Here in the years 1764-5, nearly 20,000 persons were inoculated. The Suttons claimed never to have lost a case—a claim which is suspect as they invested their methods with the secrecy of the charlatan. Their success was, however, due to such technical improvements over the methods of their contemporaries as the use of only a minute amount of virus from the vesicle rather than the pustule, the lessened danger of secondary infection where the true skin was not injured, and by the absence of dressings.

Inoculation spread rapidly to the New World. Some of the most prized of medical Americana are tracts on inoculation. Even Benjamin Franklin wrote advocating it for statistical reasons: "On the whole, if the chance were only two to one in favour of the practice among children, would it not be sufficient to induce a tender parent to lay hold of the advantage?" Dissenting voices were heard. The Reverend Edmund Massey preached a sermon at St. Andrew's Church, Boston, "against the dangerous and Sinful Practice of Inoculation",[2] and castigated satan as the first inoculator. During the American Revolution inoculation was widely employed. In Thacher's military journal occurs the following entry: "Colonel Whitcomb's regiment, consisting of 500 men has now gone through the smallpox in this town by inoculation, and except one negro, all have recovered."

It was however apparent that, although the method tended partially to control the fearful ravages of the disease, the means by which the majority of those inoculated obtained immunity were purchased at a tragic cost in human misery. For whereas an attack of inoculated smallpox was usually milder than that contracted in the usual way, the death rates reported from 1 to 10% seem fantastic to a more enlightened age. Moreover, each person inoculated was capable of infecting contacts, and the method might even result in the spread of the disease rather than in its curtailment. The danger of transmitting syphilis added to the melancholy picture. Nevertheless the evil that it succeeded in controlling to some extent was so greatly feared that if vaccination had not been discovered, inoculation might have persisted as a necessary prophylaxis. With the establishment of vaccination, inoculation rapidly became an obsolete practice and was made illegal in England in 1840.

The idea of vaccination had been germinating in several minds for some time. The country people had believed for generations that an attack of cowpox protected against smallpox. The cowpox, a disease affecting the nipples and udders of cows, was very contagious; but, although it would sweep rapidly through a herd, it was attended by no serious consequences, and was ignored by dairymen. Those who milked cows affected with the disease frequently acquired it, the evidence being a small nodule on

[1] John Baron. Life of Edward Jenner. 1838.
[2] L. H. Roddis. Edward Jenner. 1930.

the hand, the lesion going on to vesiculation and suppuration. No serious general symptoms occurred and the local lesion disappeared quickly and completely. Those who contracted cowpox were observed to be imune to smallpox. Corlett records that the beautiful Duchess of Cleveland when told that the King would desert her if her face became disfigured with smallpox replied that she was not concerned because she had had cowpox. This rural tradition was strong in Gloucestershire and attracted the attention of the young Edward Jenner who, Baron relates, often brought the subject into the local Medical Society. Apparently all of Jenner's colleagues knew of the tradition but failed to encourage or sympathize with Jenner's vision. There had been pioneer efforts in cowpox vaccination by the Dorset farmer Benjamin Jesty in 1774-89, and by Plett of Holstein in 1791. Both these attempts at vaccination were by farmers with no medical training or knowledge of science. Apparently Plett's experiment ended in severe infections. Jesty vaccinated his wife and two sons in 1774 and fifteen years afterwards one son was inoculated with smallpox with no result—the first successful vaccination of which we have record. Mrs. Jesty's vaccination nearly resulted in the loss of her arm. Jesty never repeated the experiment.

Jenner's well-deserved fame rests upon the fact that he took the countryside tradition and devoted himself for twenty-five years to observation and experiment. When the records of his work appeared he had established vaccination as a scientific method. All this was done in spite of the indifference and ridicule to which he was subjected by his fellow practitioners. When his work was done he had succeeded in carrying his inoculations successfully through several generations in the body. Moreover, he had overcome popular distrust and fear of vaccination. Entirely due to his genius and perseverance, a new working principle had been given to biological science.

Edward Jenner was born in 1749 in Berkeley, Gloucestershire. Of his early education in a school at Cirencester, his own description appears in a reply to the College of Physicians which invited him to take an examination in Latin for enrolment in the College: "The greater part of my classics has since transmigrated into heads better suited for its cultivation. At my time of life (Jenner was then sixty-four years of age), to set about brushing it up would be irksome beyond measure. I would not do it for a diadem. I would not do it for John Hunter's Museum, and that you will allow is no trifle."

At the age of thirteen, Jenner became a surgeon's apprentice in the small town of Sodbury. In 1769, he went to London to continue his medical studies under John Hunter. He soon became one of Hunter's favourite pupils. The influence of the great surgeon on young Jenner must have been tremendous. The impact of one original genius upon another bore fruit. Rejecting the opportunities for a London career afforded by the friendship and patronage of Hunter, Jenner returned to country practice in his home village in 1771. Here he became a busy practitioner respected and beloved throughout a considerable area. His many interests—literature, music, natural history, and especially ornithology, occupied his spare hours. Like his master, Hunter, he knew not idleness. But it was in the local Medical Society that the

great work which destiny allotted him began. In discussions with his colleagues, his ideas began to crystallize. He discussed cowpox and its possibilities in preventive inoculation with John Hunter whose characteristic advice was "Don't think, Jenner, try."

He set about his task by collecting all the available local data on the immunity to smallpox conferred by cowpox. He tested this immunity and observed his results year after year. Then he began cautiously to vaccinate humans and tests by subsequent inoculation with smallpox. He was able to differentiate true cowpox from other conditions simulating it and thus was able to explain some of the paradoxical results which interfered with the establishment of his thesis.

On May 14, 1796, Jenner performed his first vaccination on a boy named Phipps, from the hand of a dairy maid, Sarah Nelmes. A few weeks later, he inoculated his patient with smallpox lymph from a virulent case with no ill effects. "The Jennerian Experiment" had succeeded. The next two years were spent in collecting further data and revising the manuscript of his magnum opus. This appeared in June, 1798, as a small quarto volume of about seventy pages. Its formidable title was: "An Inquiry into the Causes and Effects of The Variolae Vaccinae, A Disease Discovered in some of the western counties of England, particularly Gloucestershire, and known by the name of the Cowpox. By Edward Jenner, M.D., F.R.S., etc."

The practice of vaccination spread with remarkable speed all over the world in spite of much opposition from both the medical profession and the laity. There were doubts as to its efficacy; jealous attempts to question the priority of Jenner's work; belittling comparisons of vaccination to the older inoculation; and untruthful reports of its use. Even the fantastic suggestion was made that the human subject if vaccinated would become cow-faced, grow horns, and low rather than talk. The greatest danger threatening "to be fatal to the infant cause of vaccination" (to use Baron's words) was the attempts of even eminent physicians to employ vaccination without taking the proper steps in obtaining, preserving, and using the virus. A formidable adversary appeared in the person of Dr. Woodville, director of the London Smallpox Hospital. He vaccinated a number of cases. These developed confluent lesions and one died. Jenner was able to show that Woodville had been vaccinating people and infecting them with smallpox at the same time.

The enthusiasm for the new safeguard against smallpox grew steadily in spite of Jenner's detractors. The Royal Jennerian Society was established in 1802. In the first 18 months, 12,000 persons were vaccinated and the yearly average of deaths from smallpox fell from 2018 to 622. The army took it up and members of the Royal Family lent their prestige to the movement. The practice spread rapidly to Germany, Italy, Greece, India and the Orient. Technical difficulties arose in the transmission of the virus for long distances. Jenner suggested the living subject as the best method of conveying the virus fresh and unimpaired. By this method, the Spanish government succeeded in sending vaccine to its colonies in the New World.

The introduction of vaccination to the North American Continent was due to a public spirited professor of medicine at Harvard, Dr. Benjamin Waterhouse. He read Jenner's Inquiry soon after publication, obtained the vaccine from

the author, and promptly vaccinated his own seven children. Three of these he then sent to the Boston Smallpox Hospital and demonstrated successfully the new prophylaxis. President Jefferson received some of the vaccine and not only his family but many of his neighbours submitted to the new method.

Overwhelming statistical proof of the efficacy of Jenner's methods came from all parts of the world and his international fame extended with amazing rapidity. Petitioners to foreign courts in the troubled war years found magic in Jenner's name. Napoleon about to refuse a petition to release some civilian prisoners saw Jenner's name and exclaimed, "Jenner! Ah, we can refuse nothing to this man."

Honors now came fast upon him. In 1813, the University of Oxford conferred upon Jenner the honorary degree of Doctor of Medicine. Not even this distinction prevailed upon the College of Physicians to include Dr. Jenner among its fellows. Recognition came not only from scientific bodies but from the courts of most of the great sovereign states. Jenner had sought no selfish end, he had allowed his practice to suffer from his devotion to his great task, he had published his results without reward to the world. In recognition of this, the Parliament of the day, 1892, honored itself by voting £10,000 to the benefactor of humanity.

Jenner had now to suffer some of the pangs of greatness. He could not but take part in the controversy which he had aroused and he found himself impelled to leave his sylvan retreat and spend much of his time in London. His correspondence was enormous. To almost all of this he attended himself. The Royal Jennerian Society founded in 1802 and replaced by the National Vaccine Institute in 1808 took much of his time. He became as he said, with no doubt a mixture of irritation and humor, a vaccine clerk to the world. His cause was rapidly winning. Misrepresentation and ridicule did not disturb his equanimity.

In 1810, the loss of his son from tuberculosis affected his health and spirits; and, from that time on, he remained for the most part at home in Berkeley and carried on his studies in ornithology. A paper on the "Migration of Birds" was published posthumously by the Royal Society in 1822. In 1815 Mrs. Jenner, long an invalid, died. Among Jenner's most marked characteristics was fondness for his family. From this shock, Jenner never fully recovered. Although the lonely and tired old physician did not relinquish his usual pursuits, he went no more to London. But even in his last few years, he maintained an unflagging interest in medical research and biology. In 1822, in his last year, he published papers on two of his favourite subjects, the uses of tartar emetic and the effects of induced eruptions on disease. All the while, he was serving his little community as a local magistrate. There in his beloved Berkeley, carrying on his part as a great servant of the community and of the world, Edward Jenner died from apoplexy on Sunday, January 26th, 1823.

Burial in Westminster was offered by a niggardly government which refused to care for the expenses. His relatives declining the offer, Jenner rests where he was most content, among the rolling hills of Gloucestershire in his natal village. London had to be content with his statue in Kensington Gardens, and a statue in Trafalgar Square.

"Vaccination," wrote Professor W. J. Simpson, in 1923, the centenary year of Jenner's death, "has saved more lives than any other preventive work in the world. Nobody realizes what conditions were before general vaccination came in. At least half a million people died yearly of smallpox in Europe. In addition to this tremendous death toll, blindness and disfigurement affected a still greater number." Few there have been in our time who would disagree—only propagandists like the late Charles Creighton, and mistaken zealots becoming ridiculous, like Bernard Shaw in his weaker moments.

Garrison's tribute is memorable: "In personality, Jenner was the typical English country gentleman, blond, blue-eyed, of handsome figure. A well-known account describes him ready for a mount in blue coat, nankeen riding-breeches, and top-boots, with whip and silver spurs. He was a bird-fancier, played the flute and violin, botanized, and wrote clever verses of which the "Address to a Robin" and the "Signs of Rain", redolent of the English countryside, deserve a place in any anthology of minor poets. Jenner's kindness of heart is seen in his regard for his first vaccination patient, James Phipps, for whom he built a cottage, planting the roses in the garden with his own hands. Like Newton, Harvey, Sydenham, Darwin, and Lister, he is one of the great men of purely Saxon genius, a happy combination of rare common sense with extreme simplicity of mind and character."[1]

[3]Garrison, F. H.. History of Medicine. W. B. Saunders. 1929.

RECENT ACCESSIONS TO THE MEDICAL READING ROOM

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ABSTRACTS

MEDICINE

Reversible Forms of Heart Disease: Briggs, J. F., Diseases of the Chest, **20:** No. 5, 482, 1951.

The author states that a heart that is normal or only slightly diseased may be adversely affected by some extracardiac condition which manifests itself entirely or largely in the cardiovascular system.

One example given is that of a 25 year old woman admitted to the obstetrical service who had previously been diagnosed as having hypertension and rheumatic heart disease. Physical examination revealed systolic and diastolic aortic murmurs, blood pressure of 180/100, and no femoral pulsations; X-rays showed notching of the ribs. The case was diagnosed as aortic coarctation and surgery produced excellent results.

Another example is obesity, which by increasing the work of the heart and by weakening the myocardium by fatty infiltration may eventually lead to right heart failure. Other conditions described are anemic and infectious states, Addison's disease and pulmonary infarction.

It is essential that these extracardiac conditions be correctly diagnosed and treated, since failure in recognition often leads to irreversible cardiac changes and ultimately death from heart failure.

G. J. Fyffe

Treatment of Hypertension with Hexamethonium Bromide: Murphy, E. A., Lancet, **2:** No. 20, 899-901, 1951.

The article deals with results obtained by using hexamethonium bromide orally or parenterally on 43 cases of hypertension of different degrees. The range of ages of the patients was 30 to 69. Some of these cases had been treated previously by sympathectomy or by potassium thiocyanate therapy without success.

The author discusses selection of cases in which no coronary disease or cerebral thrombosis was found. The majority of cases was treated with oral hexamethonium—therapy resulted in considerable improvement with patients with hypertension and retinopathy. The response was the best in those patients more severely affected, and in those with placid temperament. The minimum effective dose was 0.5 gm. b.i.d. by mouth or 25 mgm. b.i.d. by injection. In the majority of cases, blood pressures of over 190/110 fell quickly to much less severe levels.

The side-effects encountered are listed; these include constipation, light-headedness, dryness of mouth and throat, drowsiness, visual disturbances, nausea, diarrhea, and vomiting. Treatment of these side-effects is mentioned. Several investigators have attempted to demonstrate that the long-term improvement is due solely to the bromide ion; the author gives reasons why this theory is not acceptable. Apart from sleepiness, the risk of bromism is not great, and in his series only one patient showed evidence of it. Although a small number of patients become more sensitive, the majority of patients become tolerant to hexamethonium and require larger doses to maintain the fall in their hypertension.

M. Wasylenki

Infarction of the Brain without Thrombosis: Hicks, S. and Warren, S., A.M.A. Archives of Path., **52:** 5 Nov., 1951.

Apoplexy, the third leading cause of death on this continent, is the result of cerebral ischemia. That this ischemia is frequently not caused by thrombosis or hemorrhage is not generally realized. If more medical practitioners were aware of this fact, more might be done in preventive therapy for patients with prodromal symptoms of stroke.

The authors analyse a series of 100 fatal cases of cerebral infarction in which there were 60 cases without mechanical occlusion of cerebral vessels by thrombosis, embolism or arteriosclerosis and so required some other explanation for the

infarction. All forms of apoplexy (excluding aneurisms) whether chiefly hemorrhagic or chiefly infarctive have a common basis in local cerebral ischemia. In cases without mechanical occlusion this is explained as a local reduction in blood flow which on clinical and pathological bases is most probably due to vasoconstriction. The cause of this vasospasm is not clear, but it is most often associated with hypertension; in a smaller number circulatory failure or severe arteriosclerosis is present. In only a few patients could systemic circulatory failure (shock, heart failure) coupled with severe cerebral arteriosclerosis be implicated as the primary cause of the stroke.

In hypertension and in heart failure with sodium retention a complicating role is often played by cerebral edema. The pressure from the fluid in brain tissue impairs blood flow, anoxia becomes worse, ischemia ensues, edema increases, and a vicious cycle develops.

It is concluded that apoplexy is most often directly caused by cerebral vasospasm, less often by cerebral thrombosis, and least often by systemic circulatory failure, embolism, and arteriosclerosis.

J. B. Redford

SURGERY

Orbital Complications of Head Injury: Hooper, R. S., Brit. J. of Surg., **39:** No. 154, 126-138, 1951.

Derangements of the orbit affecting visual function as a major complication of head injury are discussed. The clinical features of these complications fall into three groups: deterioration or loss of vision in one or both eyes, double vision, and displacement of the eye.

There is no single constant etiological factor in the production of deterioration of vision. Blurred vision results from paralysis of the mechanism of accommodation. Defects in the visual field, however, are the commonest complications, usually severe with incomplete recovery. They occur when conduction is arrested at any point along the optic nerve by structural derangement of the orbital contents at the moment of impact, fracture of the orbital roof, optic canal, or anterior clinoid process. Hemorrhage, edema, and vascular occlusion contribute and with progressive deterioration of function after injury surgical intervention is indicated.

In the series studied, paresis of an extrinsic muscle or displacement of the globe were obvious causes of diplopia. The oculomotor nerve is more prone to damage in direct frontal blows, while the abducens is involved in those disposed more laterally. Reduction of fracture deformities, if present, should be carried out early.

Although some protrusion of the globe is usual with the development of the orbital hematoma, serious displacement may result from abscess formation, extradural hemorrhage, or herniation of brain substance. Radiology determines the cause of displacement and management presents no difficulty.

S. W. Schatz

Tenosynovitis of the Wrist: Ellis, M., B.M.J., **4734: 777** (Sept. 29) 1951.

The author has shown, in a series of 44 cases and many experiments, that the anatomical definition of this disease as an inflammation of the tendons of the abductor pollicis and extensores pollicis, producing a sausage-shaped swelling along their course, is incorrect. He finds that the swelling in no case was distal to a point 1½″ from the lower end of radius, on the dorsal surface of the forearm. The swelling is about ½″ long and slightly oblique to the long axis of the forearm. The swelling appeared too high in the forearm to have any connection with the tendons previously implicated.

A series of dissections showed conclusively that the muscle bellies and tendons of the three dorsal muscles of the thumb cross the radius obliquely in its lowest two inches. Injections of water into their sheaths produce swellings unlike those seen clinically. Also, the tendons of the extensores carpi radialis longus et brevis commence 1½″ proximal to the oblique crossing of the muscles of the thumb, and later pass in a tunnel under them. Injections into the areolar tissue

around these tendons always produce sausage-shaped swellings similar to those seen clinically in tenosynovitis. It is thus clear that the lesion is in fact in the sheath of the tendons of the extensores carpi radialis.

The causes and clinical picture are discussed. Strangely, crepitus over the inflamed sheaths is common, sometimes leading to mistaken diagnosis of fracture. Crepitus may sometimes be felt as far distally as the base of the metacarpals where the extensores carpi radialis are inserted.

There are 3 methods of treatment: rest, electrotherapy and counter-irritants. Immobilization in strap or plaster is immediately effective in relieving pain, but pain may recur immediately on cessation of treatment. Radiant heat, infra-red and short-wave diathermy have had varying success, but are not promising. Counter-irritants such as ung. iodi (B.P.), rubbed in b.i.d., while patient continues at his work, will clear up the majority of cases in 1-3 weeks.

S. Hecker

Amino Acid Therapy for Pruritis Ani: Bodkin, L. G. of Surg., 82: No. 5, 557-559. 1951.

The author postulates that pruritis ani is usually caused by an irritant from the bowel which coagulates the skin proteins. This postulation is based on observations made on post-operative patients following hemorrhoidectomy unrelated to pruritis ani. These patients were treated for superficial bleeding from granulation tissue of healing operative wounds with tannic acid ointment, which is a protein precipitant. This produced a picture much like pruritis ani.

Experiment showed that a group of chemicals which precipitated protein produced itching also. Compounds containing ammonium oleate especially, and ammonia in other forms, occasionally cause pruritis. The author suggests that more research be done into the chemical composition of feces of pruritis patients.

A rational approach to the problem would be the application of a protein upon which the irritant may act, and thus spare the skin. After trying several protein compounds, it was found that amino acid mixtures were most satisfactory. No single amino acid increased relief, but methionine and cystine made the condition much worse. A highly satisfactory preparation was made with an amino acid mixture, poor in methionine and cystine, compounded with carbowax, a high molecular weight alcohol. Relief of the itching was obtained in all but a few cases in a very few minutes. The base alone was not effective.

The patients were not suffering from pin worms or fungus infection. Most of the cases were idiopathic, but there were cases of ulcerative colitis and one case whose pruritis was caused by aureomycin.

J. A. McPhee

PEDIATRICS

Acute Subdural Hematoma in Infancy and Childhood: Fine, W. and Herson, R. N., B.M.J., 4733: 714 (Sept. 23) 1951.

The condition is essentially that of a rapid compression of the brain in young children with no evidence of trauma or hemorrhage. The urgency of such a situation necessitates prompt diagnosis and treatment to avoid fatalities.

A case report of a 13-month old girl who suddenly developed the signs and symptoms of a left upper motor neuron disturbance is outlined in some detail.

The C.S.F. findings were inconsistent with a diagnosis of subdural hemorrhage whereas the acuteness of the onset and the absence of injury were not compatible with a chronic subdural hematoma. Consideration of an acute subdural hematoma is suggested in cases where spontaneous cerebral hemorrhage cannot be fully established. Angiography is considered but is time-consuming and difficult, and treatment is imperative.

Autopsy findings by Sheldon showed that intracranial hemorrhage in a child is twice as likely to occur outside the brain as in it.

The conclusion drawn is that if a child be discovered with the signs and symptoms

of an acute, progressive intracranial lesion in which the C.S.F. findings are negative, the condition should be treated as a surgical emergency, even in the absence of a history of trauma.

B. S. Fine

OBSTETRICS

The Value of External Cephalic Version Under Anesthesia: Freeth, D. and MacVine, J., B.M.J., 4736: 881 (Oct. 13) 1951.

The object of this article is to show the results of a series of cases of version under anesthesia and to evaluate whether these results justify its use as a routine antenatal procedure. 214 cases, in all of which previous attempts at version without anesthesia had been unsuccessful, are considered. Version under anesthesia was successful in 81.3% of these cases. Since the fetal mortality due to version was 3.7% in the 79 multigravid patients, and *nil* in the 135 primigravid patients, the authors feel that version under anesthesia should be largely confined to primigravidae. Contra-indications to version are outlined.

The overall fetal mortality was 2.3% which compares favorably with the lowest fetal mortality figure for uncomplicated breech delivery reported to date, viz. the Liverpool school's 3.2% for the past 5 years. Furthermore, version under anesthesia definitely lowers the cesarian section rate, while in Liverpool this rate is exceptionally high.

The authors conclude that it should be possible to attain an 80% success rate in version under anesthesia, with a fetal mortality rate of *nil* or thereabouts attributable to the version, and that the results so obtained cannot be equalled for breech deliveries in primigravid patients in whom version using anesthesia has not been attempted.

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in the Respiratory and Circulatory Emergencies of Intravenous Barbiturate Anesthesia.

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NEWS AND NOTES

MEDICAL SOCIETY

Daffydil of 1951 opened on Dec. 17 at Hart House Theatre to an enthusiastic capacity audience. Its run was one of the longest in history—five nights. Producer Ted Nugent, Director Manny Rotenberg, and the host of other medical students who gave their time and talents to the production deserve high praise.

* * *

Medical students who participated in the Carabin Weekend, Dec. 6-9, included: Marv Auerback, Art Robertshaw, George Morrison, Dave Watson, Noreen Crocker, and Annjane Carter of Meds 5T2; Harry Abramowitz of Meds 5T4, and Dorothy Lieberman and Freda McQueen of Meds 5T6. Miss Lieberman was the chairman of the committee that organized the Weekend, and is to be commended on the success of the visit.

* * *

This year, in support of the University Red Feather Campaign, the Medical Society arranged to have a technicolor film depicting the activities of eight of the sixty-six Red Feather Agencies shown to all six medical and premedical years. The students who saw the film were sufficiently impressed by it to give most generously to the campaign.

* * *

At the November meeting of the Osler society, two papers were presented. Ron Tasker discussed the incidence and effect of magic and religion in the medical practices of primitive tribes; Doug Abbey, speaking on personalities in Medicine in Western Canada, told many anecdotes from the lives of the pioneer physicians.

* * *

Two thought-provoking debates, sponsored by the Medical Arts and Letters Club, were held in two noon-hour periods, and were well attended by students from Medicine and other faculties. The subjects were of general interest, and calculated to arouse discussion. Both resolutions, first, "That women have no place in the Faculty of Medicine", and the second, "That Euthanasia should be legalized by the Medical Profession", were defeated.

* * *

The Annual Banquet of the Alpha of Ontario chapter of the Alpha Omega Alpha Honor Medical Fraternity was held at the King Edward Hotel on November 26. Chairman was Mr. R. R. Tasker, and guest speaker, Dr. B. Wilkinson, from the Department of History, University of Toronto.

* * *

The Medical Society has established a "common-room" committee under the chairmanship of the Society vice-president, Fraser Mustard, to look into the question of establishing one or more well-equipped common rooms for the use of medical students who are now severely hampered by lack of space in the old T.G.H. "Common Room".

FACULTY

The Phi Delta Epsilon medical lecture was delivered on December 3rd by Dr. Henry Bockus of Philadelphia. Faculty members, graduates, and students were stimulated by Dr. Bockus' clear, forceful presentation of his subject: "Functional Disorders of the Gastro-intestinal Tract".

* * *

On December 3rd, the fourth medical year was privileged to hear Dr. Morris McPhedran of Philadelphia, son of the late Professor Alexander McPhedran, lecture on some aspects of pulmonary tuberculosis. Dr. McPhedran also left with the class some stimulating thoughts on the way in which research in vitamins might be pursued.

* * *

Dr. D. R. Mitchell, Associate Professor of Surgery, is the president-elect of the Northeastern section of the American Urological Association.

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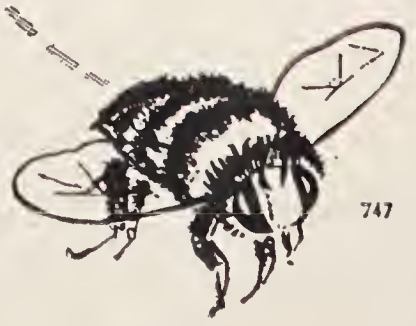

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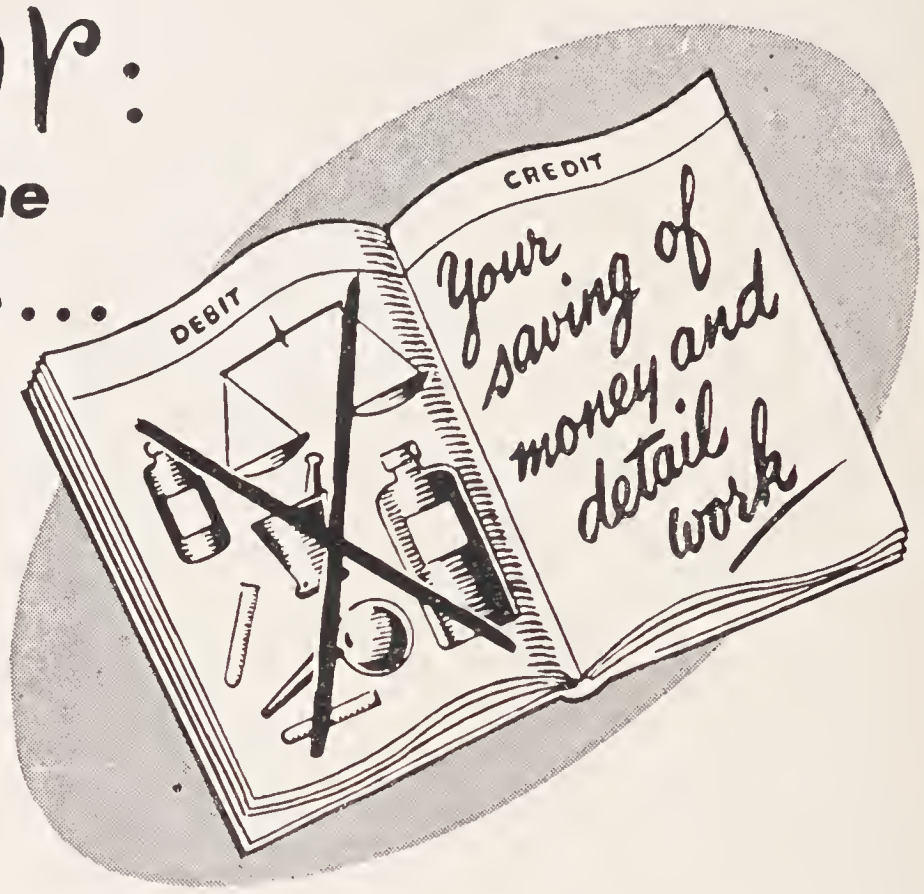

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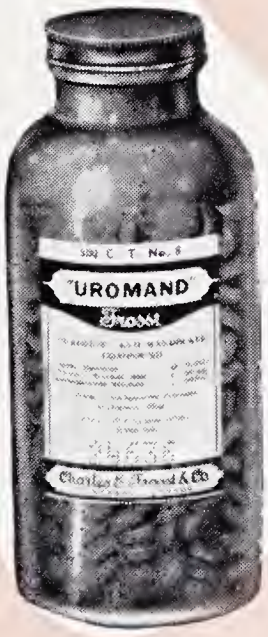

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Urosine (brand of Hexamine)	1¼ gr. (80 mg.)
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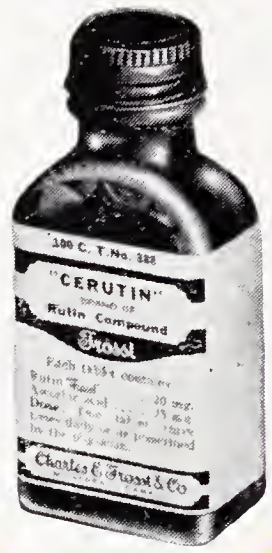
Brand of Rutin with Vitamin C



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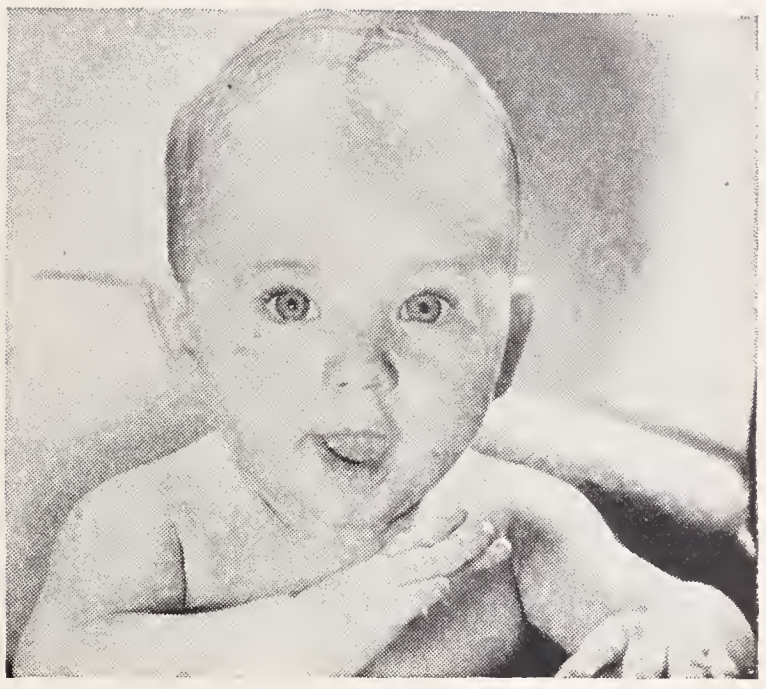
Baby A—2 weeks



Baby B—5½ months

Which baby would you put on meat?

ANSWER: *BOTH! 2 to 3 months is common . . . and some physicians start at 2 weeks in formula!*

Commonly meat is being fed at 2 to 3 months. In a recent survey among mothers feeding meat, the majority said their doctors recommended starting meat along with first solid foods!

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At Six Weeks: Increasing protein intake 25% by the addition of Swift's Meats for Babies to formula promoted hemoglobin and red blood cell formation: *Leverton and Clark, "Meat in the Diet of Young Infants," J. Am. Med. Assn., 134,* 1215, (1947).

With Allergy Cases: A formula of Swift's Meats for Babies enriched with minerals, fat, and carbohydrate offers an effective milk substitute for infants allergic to milk proteins: *McQuarrie and Ziegler, "Nutritive Value of Mineral-Enriched Meat and Milk," Pediatrics, 5,* 210, (1950).

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Two potencies are available:

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"Cillenta" Liquid 50 (yellow) — When dissolved as directed (to produce 2 fluid ounces), each teaspoonful will contain 50,000 I.U. Penicillin G potassium (crystalline).

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Suggested Therapeutic Dosage
(given at three-hourly intervals)

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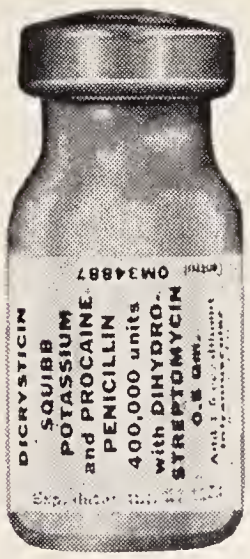

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1. Swan, K. C.: Tr. Am. Acad. Ophth. & Otolaryng.; March-April 1951, p. 406.
2. Theodore, F. H.: J.A.M.A. *143*:226 (May 20) 1950.

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